1-Aryl-3-(4-pyridine-2-ylpiperazin-1-yl)propan-1-one Oximes as Potent Dopamine D_4 Receptor Agonists for the Treatment of Erectile Dysfunction

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A new series of dopamine D_4 receptor agonists, 1-aryl-3-(4-pyridinepiperazin-1-yl)propanone oximes, was designed through the modification of known dopamine D_4 receptor agonist PD 168077. Replacement of the amide group with a methylene-oxime moiety produced compounds with improved stability and efficacy. Structure–activity relationsips (SAR) of the aromatic ring linked to the *N*-4-piperazine ring confirmed the superiority of 2-pyridine as a core for D_4 agonist activity. A two-methylene linker between the oxime group and the *N*-1-piperazine ring displayed the best profile. New dopamine D_4 receptor agonists, exemplified by (*E*)-1-(4-chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-methyloxime (**59a**) and (*E*)-1-(3-chloro-4-fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-methyloxime (**64a**), exhibited favorable pharmacokinetic profiles and showed oral bioavailability in rat and dog. Subsequent evaluation of **59a** in the rat penile erection model revealed in vivo activity, comparable in efficacy to apomorphine. Our results suggest that the oximes provide a novel structural linker for 4-arylpiperazine-based D_4 agonists, possessing leadlike quality and with potential to develop a new class of potent and selective dopamine D_4 receptor agonists.

Introduction

Erectile dysfunction (ED) is defined as the inability of the male to achieve and maintain a penile erection sufficient for adequate sexual intercourse. ED affects 20 to 30 million men in the United States and over 150 million men worldwide.[1] Pharmacological treatment of ED has been revolutionized since the introduction of sildenafil, an orally active PDE5 inhibitor.[2] Two other phosphodiesterase (PDE5) inhibitors, tadalafil[3] and vardenafil,[4] have been approved recently for the treatment of ED. These drugs can improve erections in >60% of men. However, there are populations of patients who have low incidence of erections or have contraindications to the use of PDE5 inhibitors.[5]

Penile erection is regulated by peripheral factors and by the central nervous system. The physiology of penile erection was extensively reviewed.[6–9] Sildenafil and two other PDE5 inhibitors are representatives of the peripherally acting drugs. Dopamine is one of the major modulatory neurotransmitters in the central nervous system (CNS) responsible for the control of sexual function.[6,10] Two families of dopamine receptors have been identified.[11,12] The D_1-like family consists of D_1 and D_5 receptors, is Gs-coupled, and activates adenylate cyclase. The D_2-like family consists of D_2, D_3, and D_4 receptors, is Gi-coupled, and inhibits adenylate cyclase. Apomorphine is a nonselective dopamine D_2-like receptor agonist and exhibits efficacy in patients suffering ED.[13]

We have reported that the dopamine D_4 receptor subtype activity is responsible for the erectogenic property of apomorphine and that the D_2 receptor subtype activity is responsible for the side effects of apomorphine, like nausea and emesis.[14,15] The culmination of our efforts was discovery of **1**, a selective D_4 agonist that facilitates penile erection in rats.[16,17]

Selective D_4 agonists may also have a therapeutic indication in ADHD (attention deficit with hyperactivity disorder), memory consolidation, or novelty seeking.[18–21] Therefore, our quest for a new structurally diverse class of selective D_4 agonists has continued. Most research in the D_4 area has focused on discovery of selective D_4 antagonists,[18] because of the antipsychotic activity of clozapine (a preferential D_4 antagonist). Only a few selective D_4 agonists **1**–**7** have been described in the literature (Chart 1). Compounds **2** and **3** were the first reported selective D_4 agonists.[22–24] Recently, four other compounds **4**–**7** were described as selective dopamine D_4 receptor agonists.[25–28] The agonists **5** and **6** were less efficacious (36% and 31%, respectively) in functional assays than the recently described agonist **4** (% E = 83). The fourth one, **7**, was a potent D_4 agonist (EC_{50} = 50 nM) and showed high efficacy (83% vs 100% efficacy of quinpirole).[28]

Our strategy to design the next generation of selective D_4 agonists was to start from the known D_4 agonist and make such structural modifications that the D_4 agonist efficacy would be preserved in the emerging new class of compounds.

We selected **2** (EC_{50} = 8.3 nM, % E = 60), a selective D_4 agonist (>100-fold selectivity over D_1, >300-fold over D_3, and >400-fold over D_2 receptor, 20-fold selectivity over α_1- and α_2-adrenoceptors, 45-fold selectivity over $5HT_{1A}$, and 460-fold selectivity over $5HT_{2A}$)[23] as our starting point. Modification of the link between aryl and piperazine rings led to the oxime series (Chart 2), showing good agonist activity at D_4 receptors. First, to improve the stability of **2** and its analogues (as aminals, they have a limited stability in acidic conditions[22]), we replaced the amide group with a methylene-keto group to get ketone. However, because of carbonyl group metabolic liability,[29,30] we transformed the keto group into an oxime to obtain a novel class of potent and efficacious dopamine D_4 agonists.

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Chart 1. Dopamine D_4 Receptor Agonists Reported in Literature

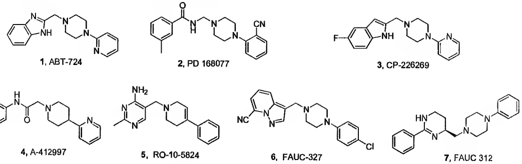
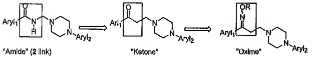


Chart 2. Amide to Oxime Replacement Approach to Obtain Novel D_4 Agonists



Chemistry

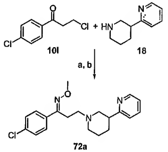
Mannich reaction[31,32] of alkyl aryl ketones **9a–w** with 1-arylpiperazines (**13a,b**, **15a**) and paraformaldehyde in the presence of acid gave piperazinylpropanone derivatives ("ketones"). The partially purified "ketones" were condensed with hydroxylamine or *O*-alkylhydroxylamine in pyridine to provide oximes (**17–30**, **38–40**, **73**, **75**) or *O*-alkyloximes (**31–37**, **41–71**, **74**, **76**, **85a**), respectively. In the case of commercially available β-chloropropiophenones, the piperazinylpropanone analogues were prepared by direct condensation of β-chloropropiophenones (**10a–c**, **11**, **12**) with 1-arylpiperazines (**13c–l**, **14**, **15b**) in *N*,*N*-dimethylformamide (DMF) in the presence of inorganic base or by refluxing of β-chloropropiophenone in toluene with 2 equiv of 1-arylpiperazine.[33] (Scheme 1) Some *O*-alkyloximes **32–37** were also prepared by alkylation of an oxime with an appropriate alkyl halide in the presence of potassium *t*-butoxide.[34]

The oximes with one (**73**, **74**) or three (**75**, **76**) methylene links were prepared by condensation of α-haloacetophenone **11** or γ-chlorobutyrophenone **12** with piperazine derivatives, followed by reaction with *O*-methylhydroxylamine as described for two-methylene link analogues. All of the arylpiperazines were commercially available except for 3-methyl-1-pyridin-2-ylpiperazine, which was synthesized by reaction of 2-bromopyridine with 2-methylpiperazine at 120 °C for 18 h. The oximes with 4- (**70**, **71**) and 3-piperidine (**72a**) cores were prepared as described for piperazine-based analogues. The appropriate 4- (**15a,b**) or 3-arylpiperidines **16** were prepared as described in the literature.[18,35–37] These were transformed into oxime derivatives by using procedures applied for the preparation of arylpiperazine analogues as depicted in Schemes 1 and 2.

α-Hydroxyketones were prepared from the crude 1-aryl-3-(4-arylpiperazin-1-yl)propan-1-ones by treatment with iodobenzene diacetate in basic methanol as reported in the literature.[38] Reaction with hydroxylamine or *O*-alkylhydroxylamine gave the desired α-hydroxyoximes **79a,b** or *O*-alkyloximes (**77a,b**, **84ab**) (Scheme 3).

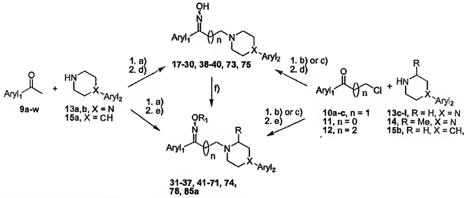
The α-methoxy analogues (**78a,b**, **80a,b**) were isolated as side products of the hydroxylation reaction. Both α-hydroxy and α-methoxy derivatives reported in this paper were tested as racemates.

Scheme 2[a]



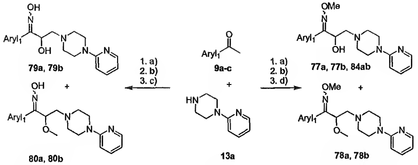
[a] Reagents and conditions: (a) K_2CO_3, DMF, RT; (b) $MeONH_2 \cdot HCl$, pyridine.

Scheme 1[a]



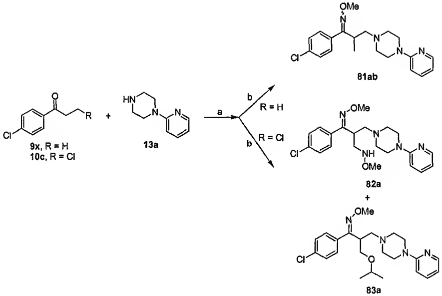
[a] Reagents and conditions: (a) *N*-arylpiperazine, $(CH_2O)_n$, *i*-PrOH, concentrated HCl, reflux; (b) $n = 0, 1, 2$, K_2CO_3, DMF, RT; (c) $n = 1.2$ equiv of *N*-arylpiperazine, toluene, reflux; (d) $HONH_2 \cdot HCl$, pyridine; (e) $RONH_2 \cdot HCl$, pyridine; (f) *t*-BuOK, *t*-butanol, R–X, reflux.

Scheme 3[a]



[a] Reagents and conditions: (a) $(CH_2O)_n$, *i*-PrOH, concentrated HCl, reflux; (b) (1) $PhI(OAc)_2$, KOH, MeOH, RT, (2) 5% H_2SO_4, $CHCl_3$, RT; (c) $H_2NOH{\cdot}HCl$, pyridine; (d) $H_2NOMe{\cdot}HCl$, pyridine.

Scheme 4[a]



[a] Reagents and conditions: (a) $(CH_2O)_n$, *i*-PrOH, concentrated HCl, reflux; (b) $MeONH_2{\cdot}HCl$, pyridine, RT.

α-Methyl analogue **81ab** was prepared by condensing 4-chlorophenyl ethyl ketone **9x** with 4-(2-pyridyl)piperazine **13a** by the described Mannich procedure. Mannich reaction of 3,4′-dichloropropiophenone **10c** followed by reaction with *O*-methylhydroxylamine provided **82a** and **83a** (Scheme 4).

Results and Discussion

All of the synthesized compounds were first tested for their functional activity at D_4 receptor in a calcium flux assay (FLIPR), by use of recombinant human $D_{4.4}$ receptor coexpressed with chimeric $G\alpha_{qo5}$ proteins in HEK-293 cells as described in the literature.[39] The results represent compound agonist efficacy and compound potency and are shown in the tables. The agonist efficacy is presented as the maximal efficacy of agonist in comparison to 10 μM dopamine (100%). Compound potency is expressed as an EC_{50} value, a concentration giving half the maximal receptor stimulation. The compounds were also tested for D_2 agonist activity in a similar FLIPR assay but by use of recombinant human D_{2L} coexpressed with chimeric $G\alpha_{qo5}$ proteins in HEK-293 cells.[39] D_4 ligand binding affinity was determined by radioligand competition against [^{3}H]-A-369508,[40] with membranes from the engineered HEK-293 cells. D_2 binding affinity was determined by use of the D_2-like agonist radioligand [^{125}I]-PIPAT on human D_{2L} expressed in HEK-293 cells.

In earlier publications,[17,41] it was demonstrated that the presence of a 2-pyridine moiety in the 4-position of piperazine (aryl$_2$ group) provided D_4 agonists with good potency and efficacy. And indeed, a modification of **2** by replacement of 2-cyanophenyl group with 2-pyridyl group provided a compound **8** with better efficacy (71% vs 60% for **2**) and almost the same potency (EC_{50} = 12.9 nM vs 8.3 nM for **2**) (Chart 3).

Replacement of the amide moiety of **8** with the methyleneoxime group (Chart 2) provided **22a**, the prototype 1-aryl-3-(4-pyridinepiperazin-1-yl)propanone oxime. This compound was a potent D_4 agonist (EC_{50} = 2.3 nM vs 8.3 nM for **2** vs 12.9 nM for **8**) with efficacy (74%) comparable to **8** (71%) and **2** (60%). The compound's structure was confirmed by X-ray crystallography to be the *E*-isomer (Chart 4).

The encouraging results prompted us to further explore the structure–activity relationships (SAR) describing D_4 agonism in this series. SAR of phenyl substitution (aryl$_1$ group) (Table 1) revealed that both *E*- and *Z*-isomers of oximes with unsubstituted or monosubstituted phenyl with electron-donating

Chart 3. 2-Cyanophenyl to 2-Pyridyl Replacement

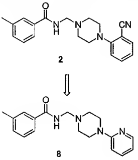


Chart 4. X-ray Crystal Structure of **22a**

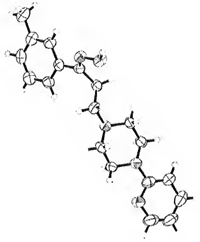
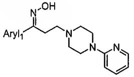


Table 1. Oxime–Phenyl Ring Substitution SAR

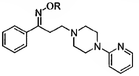


compd	isomer	aryl$_1$	human D_4 FLIPR EC_{50},[a] nM	human D_4 FLIPR % E[b]
17a	*E*	phenyl	4.4 ± 0.2	70
17b	*Z*	phenyl	21.7 ± 1.8	74
18a	*E*	2-chlorophenyl	24 ± 1	74
18b	*Z*	2-chlorophenyl	25 ± 1	64
19a	*E*	2-methylphenyl	4.2 ± 0.2	82
19b	*Z*	2-methylphenyl	20.3 ± 0.4	72
20a	*E*	3-fluorophenyl	17.1 ± 0.7	72
21a	*E*	3-chlorophenyl	11.9 ± 0.7	73
22a	*E*	3-methylphenyl	2.3 ± 0.7	74
23a	*E*	3-cyanophenyl	13.1 ± 0.2	48
24a	*E*	4-fluorophenyl	31 ± 10	74
25a	*E*	4-chlorophenyl	475 ± 110	46
26a	*E*	3,5-difluorophenyl	19.4 ± 0.3	74
26b	*Z*	3,5-difluorophenyl	17.5 ± 0.4	70
27a	*E*	3,5-dimethylphenyl	45.8 ± 0.7	55
28a	*E*	2,4-difluorophenyl	8.9 ± 0.7	78
29a	*E*	2-benzyloxy-5-methylphenyl	> 10 000	4
30a	*E*	2-hydroxy-5-methylphenyl	19.2 ± 0.3	73

[a] Mean values for agonists (SEM, $n \geq 3$). [b] Efficacy relative to 10 μM dopamine (100%).

groups showed good potencies (EC_{50} ranging between 2.3 nM for **22a** and 31 nM for **24a**). The exception was **25a**, where *p*-chloro substitution substantially decreased the potency (EC_{50} = 475 nM) of the agonist. Since *Z*-isomers were minor products

Table 2. SAR of *O*-Alkyl Group of O-Substituted Oximes



compd	isomer	R	human D_4 FLIPR EC_{50},[a] nM	human D_4 FLIPR % E[b]
17a	*E*	H	4.4 ± 0.2	70
17b	*Z*	H	21.7 ± 1.8	74
31a	*E*	Me	32 ± 1	87
31b	*Z*	Me	24.1 ± 0.3	85
32a	*E*	Et	28.5 ± 0.5	85
32b	*Z*	Et	45 ± 15	73
33a	*E*	*n*-Pr	320 ± 99	64
34a	*E*	Bu	382 ± 16	76
35a	*E*	*i*-Pr	164 ± 34	83
36a	*E*	allyl	350 ± 100	69
37a	*E*	CH_2CN	33 ± 4	75

[a] Mean values for agonists (SEM, $n \geq 3$). [b] Efficacy relative to 10 μM dopamine (100%).

of the reaction, only limited examples were characterized. The EC_{50} of *Z*-isomers **17b** and **19b** were 5 times less potent than their *E*-counterparts **17a** and **19a**, respectively. The EC_{50} value of the *Z*-analogue **18b** was equipotent to that of the *E*-isomer **18a**.

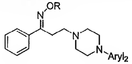
The efficacies of *E*- and *Z*-isomers of unsubstituted or monosubstituted phenyl with electron-donating groups showed comparable values with the exception of **23a**, having an electron-withdrawing cyano group in meta position (48% efficacy). Another exception was the *p*-chloro analogue **25a**, which had exhibited reduced potency, also displayed only 46% efficacy.

The efficacies as well as potencies of disubstituted phenyl analogues were substantially affected by the bulkiness of the second substituent (**29a** vs **30a** vs **22a** or **27a** vs **22a**), whereas analogues with two fluorines exhibited potencies and efficacies comparable to monofluoro-substituted analogues (**26a** vs **20a** and **28a** vs **24a**). In general, the lack of *E*/*Z* selectivity in efficacy was observed for unsubstituted or monosubstituted Aryl$_1$ congeners as well as for disubstituted aryl$_1$ analogues. Consequently, **22a** emerged as the most potent compound (EC_{50} = 2.3 nM) within the oxime analogues, whereas **19a** emerged as the most efficacious analogue (% E = 82). O-Alkylated oxime analogues were also examined. First, we evaluated an effect of alkyl chain elongation in *O*-alkyl analogues on D_4 receptor efficacy and potency. (Table 2).

As shown in Table 2, *O*-methyl, both *E*- and *Z*-isomers **31a** and **31b**, and *O*-ethyl *E*-isomer **32a** gave agonists with the highest potency and efficacy. Increasing the size of alkyl group resulted in a drop of potency, except for cyanomethyl analogue **37a**, and in a drop of efficacy except for **35a**. The better potency of **35a** than its isomer **33a** indicates that an *O*-alkyl group with a two-carbon chain is preferred and that elongation of chain to three-carbon or more leads to a decrease in potency and efficacy (see also **34a**, **36a**). Subsequently, only oximes or their *O*-methyl- or *O*-ethyl derivatives were used in the further SAR studies.

Since our SAR studies of oximes started with the 2-pyridyl derivative **22a**, we decided to reexamine the aryl and heteroaryl substituents in the 4-position of piperazine (aryl$_2$ group). As evident in Table 3, replacement of the 2-pyridine ring in **17a** with 3-substituted pyridine (**38a** and **38b**) or other heterocycles (**39a**, **39b** or **40a**) resulted in a 4–12-fold drop in potency

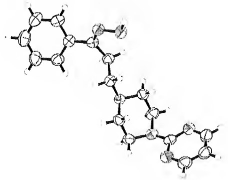
Table 3. SAR of 4-Piperazine Substitution (Aryl$_2$ Group)



				human D$_4$ FLIPR	
compd	isomer	R	aryl$_2$	EC$_{50}$,[a] nM	% E[b]
17a	*E*	H	2-pyridine	4.4 ± 0.2	70
38a	*E*	H	3-cyano-2-pyridine	18 ± 1	64
38b	*Z*	H	3-cyano-2-pyridine	20 ± 1	49
39a	*E*	H	2-pyrimidine	39.2 ± 10.4	49
39b	*Z*	H	2-pyrimidine	69 ± 22	52
40a	*E*	H	2-thiazole	49.5 ± 14.6	44
32a	*E*	Et	2-pyridine	28.5 ± 0.5	86
41a	*E*	Et	phenyl	109 ± 38	80
42a	*E*	Et	2-cyanophenyl	48.7 ± 16.9	82
43a	*E*	Et	2-methoxyphenyl	338 ± 82	76
44a	*E*	Et	3-methoxyphenyl	2680 ± 1230	30
45a	*E*	Et	4-methoxyphenyl	>10 000	5
46a	*E*	Et	2-ethoxyphenyl	347 ± 66	84
47a[c]	*E*	Me	2-isopropoxyphenyl	594 ± 46	46
47b[c]	*Z*	Me	2-isopropoxyphenyl	601 ± 60	59
48a	*E*	Et	3-cyano-2-pyridine	139 ± 38	64
49a	*E*	Et	3-methyl-2-pyridine	253 ± 91	49
50a	*E*	Et	2-pyrimidine	615 ± 189	26
51a	*E*	Et	2-thiazole	81.8 ± 0.6	72

[a] Mean values for agonists (SEM, $n \geq 3$). [b] Efficacy relative to 10 μM dopamine (100%). [c] 4-Fluorophenyl group instead of phenyl group.

Chart 5. X-ray Crystal Structure of **39a**



accompanied by a significant reduction of efficacy. The pyrimidine analogue **39a** showed almost a 10-fold drop in potency and 30% drop in efficacy when compared to its pyridine analogue **17a**.

The X-ray-crystallography of selected pyridine-based oximes **22a**, **25a**, and **75a** and pyrimidine-based oxime **39a** revealed that the pyridine ring is positioned in pseudoequatorial orientation (see X-ray structure of **22a** in Chart 4), whereas the pyrimidine ring is in pseudoaxial orientation (see X-ray structure of **39a** in Chart 5). The pseudoaxial orientation could increase steric and electronic interactions between the pyrimidine in 4-position and propanone oxime group in 1-position of piperazine, which could negatively affect the potency and efficacy of pyrimidine analogue. As we noticed before, both *E*- and *Z*-isomers showed comparable potency and efficacy within oxime analogues. In the case of *O*-alkyl-substituted analogues, replacing the 2-pyridyl group in **32a** with a phenyl moiety lead to a compound **41a** with good efficacy (% E = 80), but >3 times weaker potency (EC$_{50}$ = 109 nM).

Similar to the aryl$_2$ SAR we have seen in other D$_4$ series,[41,42] the unsubstituted phenyl analogue (**41a**) and ortho-substituted phenyl compounds (**42a**, **43a**, **46a**) retained good efficacy. However, their potencies decreased with increasing size of the ortho substituent (**41a** vs **43a** vs **46a** vs **47a**), with an *o*-isopropoxy group affecting not only potency but also efficacy (see **47a,b**). The only exception was *o*-cyano substitution, which gave a compound **42a** with potency and efficacy similar to **32a**. The increasing size of ortho substituent probably forces a pyridine ring into a less favorable axial orientation (as described for pyrimidine analogue **39a**), resulting in lower potency and efficacy. The meta-substituted analogue **44a** had low efficacy (% E = 30) and a very low potency (EC$_{50}$ = 2.7 μmol), whereas para-substituted analogue **45a** was inactive. Substitution of pyridine in **32a** in 3-position with a cyano group led to **48a**, showing lower efficacy (% E = 64) and 5-fold drop in potency, whereas the 3-methyl group substitution in **49a** provided an analogue with even lower potency and efficacy than 3-cyano substitution. Replacing of 2-pyridine in **32a** with 2-pyrimidine (**50a**) resulted in almost complete loss of agonist activity (% E = 26).

The possible pyrimidine–oxime interactions in pyrimidine-based oxime should increase with oxime substitution, and indeed **50a**, the *O*-ethyl analogue of **39a**, showed a 15-fold drop in potency (IC$_{50}$ = 601 nM vs 39 nM for **39a**) and a 2-fold drop in efficacy (26% vs 49% for **39a**). The 2-thiazole–pyridine replacement in **32a** afforded a compound **51a** with lower efficacy (72% vs 86% for **32a**) and almost 3 times lower potency than **32a**, indicating that the thiazole ring has a different orientation than pyrimidine or that the smaller ring, like thiazole, is tolerated even in the pseudoaxial orientation.

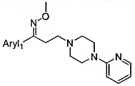
In general, only the 2-cyanophenyl group provided analogue **42a** with potency and efficacy values similar to the pyridine analogue **32a**. In conclusion, the highest efficacy and the best potency for oximes as well as for *O*-alkyloximes were found for analogues **17a** and **32a** having unsubstituted pyridine as the aryl$_2$ moiety.

On the basis of the above results, analogues with unsubstituted pyridine as aryl$_2$ were selected for further SAR studies. We demonstrated in Table 1 the effect of aryl$_1$ group substitution for oximes, and now the effect of phenyl ring (aryl$_1$) substitution for *O*-methyl-substituted oximes was reexamined.

As shown in Table 4, in the case of *O*-methyloximes (both *E*- and *Z*-isomers), aryl$_1$ unsubstituted and monosubstituted phenyl analogues showed very good agonist potency (EC$_{50}$ ranging between 13 and 89 nM), except for **55b** and **60a**, which had EC$_{50}$ > 100 nM. We could not identify a specific aryl$_1$ substitution pattern controlling potency of *E*- and *Z*-isomers within *O*-methyl analogues. Only for 3-substituted phenyl with electron-donating groups were *E*-isomers (see **54a**, **55a**, and **56a**) more potent than their *Z*-counterparts (**54b**, **55b**, and **56b**). The efficacy in general was very high, and agonists **56a**, **58a**, and **59a** showed almost full efficacy. All *E* isomers of *O*-methyloximes were only slightly more efficacious than analogous *Z*-isomers except for **54b** (aryl$_1$ = 3-fluorophenyl) and **57b** (aryl$_1$ = 3-cyanophenyl) agonists. The potency but not the efficacy of disubstituted phenyl analogues was affected more significantly, except for *E*- and *Z*-3,5-difluoro analogues **61a,b**. Most disubstituted *Z*-isomers showed higher potency than the analogous *E*-isomers (with the exception of **61b** and **63b**), even if the efficacy of *Z*-isomers was on average 10% lower than that of *E*-isomers. Replacement of phenyl group with 3-pyridine provided a compound **68ab** with activity as good as phenyl analogues, indicating that heterocycles could be also tolerated as aryl$_1$ group. The compound was tested as an *E*/*Z* mixture since the attempts to separate of isomers were unsuccessful.

We showed earlier that **25a**, an oxime with aryl$_1$ *p*-chloro substituent, showed a dramatic loss of potency (EC$_{50}$ = 475

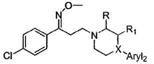
Table 4. Phenyl Ring Substitution in *O*-Methyloximes



			human D_4 FLIPR	
compd	isomer	aryl$_1$	EC_{50},^{a} nM	% E^b
31a	*E*	phenyl	32 ± 1	89
31b	*Z*	phenyl	24.1 ± 0.3	85
52a	*E*	2-chlorophenyl	42.3 ± 0.6	79
52b	*Z*	2-chlorophenyl	57.2 ± 10.7	73
53a	*E*	2-methylphenyl	74 ± 13	80
53b	*Z*	2-methylphenyl	40.1 ± 0.8	72
54a	*E*	3-fluorophenyl	44.6 ± 0.2	76
54b	*Z*	3-fluorophenyl	60.2 ± 10.3	79
55a	*E*	3-chlorophenyl	88.9 ± 13.2	80
55b	*Z*	3-chlorophenyl	113 ± 18	69
56a	*E*	3-methylphenyl	27.6 ± 0.5	84
56b	*Z*	3-methylphenyl	61 ± 1	75
57a	*E*	3-cyanophenyl	63.7 ± 0.9	63
57b	*Z*	3-cyanophenyl	27.5 ± 0.5	70
58a	*E*	4-fluorophenyl	48.8 ± 0.3	87
58b	*Z*	4-fluorophenyl	13.6 ± 0.2	79
59a	*E*	4-chlorophenyl	37.6 ± 0.5	87
59b	*Z*	4-chlorophenyl	56.6 ± 16.3	68
60a	*E*	4-bromophenyl	183 ± 44	72
60b	*Z*	4-bromophenyl	82 ± 12	64
61a	*E*	3,5-difluorophenyl	37.2 ± 0.8	92
61b	*Z*	3,5-difluorophenyl	46.7 ± 0.4	86
62a	*E*	3,5-dimethylphenyl	175 ± 66	71
62b	*Z*	3,5-dimethylphenyl	74.7 ± 17.4	83
63a	*E*	2,4-dichlorophenyl	249 ± 55	78
63b	*Z*	2,4-dichlorophenyl	296 ± 35	65
64a	*E*	3-chloro-4-fluorophenyl	148 ± 21	85
64b	*Z*	3-chloro-4-fluorophenyl	95 ± 17	71
65a	*E*	3,4-dichlorophenyl	542 ± 37	79
65b	*Z*	3,4-dichlorophenyl	341 ± 49	63
66a	*E*	4-chloro-3-methylphenyl	135 ± 11	89
66b	*Z*	4-chloro-3-methylphenyl	98 ± 26	79
67a	*E*	3,4-dimethylphenyl	108 ± 26	82
67b	*Z*	3,4-dimethylphenyl	91 ± 10	71
68ab^c	*E*/*Z*	3-pyridyl	33.3 ± 0.7	82

^{a} Mean values for agonists (SEM, $n \geq 3$). ^{b} Efficacy relative to 10 μM dopamine (100%). ^{c} 5:2 Mixture of *E*:*Z* isomers.

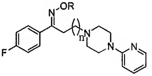
Table 5. SAR of the Central Ring



						human D_4 FLIPR	
compd	isomer	R	R$_1$	aryl$_2$	X	EC_{50},^{a} nM	% E^b
59a	*E*	H	H	2-pyridine	N	37.6 ± 0.5	87
59b	*Z*	H	H	2-pyridine	N	56.6 ± 16.3	68
69a	*E*	Me	H	2-pyridine	N	333 ± 39	60
69b	*Z*	Me	H	2-pyridine	N	99 ± 14	45
70a	*E*	H	H	2-pyridine	CH	195 ± 100	54
70b	*Z*	H	H	2-pyridine	CH	> 10 000	10
71a	*E*	H	H	2-pyridine N-oxide	CH	84 ± 24	77
71b	*Z*	H	H	2-pyridine N-oxide	CH	46.4 ± 0.9	65
72a	*E*	H	2-pyridine	H	CH_2	606 ± 71	48

^{a} Mean values for agonists (SEM, $n \geq 3$). ^{b} Efficacy relative to 10 μM dopamine (100%).

Table 6. Effect of Length of the Linker



				human D_4 FLIPR	
compd	isomer	R	n	EC_{50},^{a} nM	% E^b
73a	*E*	H	0	> 10000	32
73b	*Z*	H	0	26 ± 1	49
74a	*E*	Me	0	4290 ± 1160	26
74b	*Z*	Me	0	43.8 ± 0.7	74
24a	*E*	H	1	31 ± 1	74
58a	*E*	Me	1	48.8 ± 0.3	87
58b	*Z*	Me	1	13.6 ± 0.2	79
75a	*E*	H	2	9.5 ± 2.5	62
75b	*Z*	H	2	59.3 ± 1.6	65
76a	*E*	Me	2	41.7 ± 0.9	60
76b	Z	Me	2	33.5 ± 1.2	59

^{a} Mean values for agonists (SEM, $n \geq 3$). ^{b} Efficacy relative to 10 μM dopamine (100%).

nM) and efficacy (% $E = 46$) compared to the *o*- and *m*-chloro analogues (see Table 1). Alkylation of the oxime with a methyl group restored the potency ($EC_{50} = 38$ nM) and efficacy (% $E = 87$) of **59a** (see Table 4). This unexpected result could imply that the more rigid structure of **25a**, if we assume an internal hydrogen bond of oxime with the nitrogen of piperazine, is forcing a chlorine atom in less favorable orientation. O-methylation of oxime **25a** would eliminate this intramolecular hydrogen bond and lead to a more favorable orientation of chlorine in the binding pocket.[43,44]

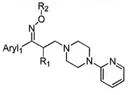
The nature of the central ring was also important for activity. As shown in Table 5, replacement of piperazine ring with 2-methylpiperazine (**69a,b**), 4-piperidine (**70a,b**), or 3-piperidine (**72a**) resulted in profound loss of potency and efficacy. The potency and efficacy of *E*-isomer **70a**, a 4-piperidine analogue of **59a**, dropped very significantly and its *Z*-isomer **70b** became completely inactive. The replacement of piperazine ring with 3-piperidine ring gave even more dramatic results than with the 4-piperidine replacement. A 3-(2-pyridyl)piperidine analogue, *E*-isomer **72a** (a 1,3 regioisomer of **70a**), showed more than 3-fold loss of potency ($EC_{50} = 606$ nM for **72a** vs 195 nM for **70a**) even though their efficacies remained almost the same.

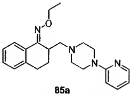
The drop in potency and efficacy of **70a**, a 4-piperidine analogue of **59a**, could be attributed to the axial orientation of the polar pyridinyl group in the 4-position of the piperidine ring. For the polar 4-substituents of piperidine, the axial orientation is favored.[45] On the other hand, the oxidation of pyridine to its N-oxide would force the larger pyridine N-oxide back into an equatorial position. This should result in pyridine N-oxide–piperidine conformation similar to pyridine–piperazine analogues. And indeed, as we expected, the D_4 potency and efficacy were restored. Both *E*-isomer **71a** and *Z*-isomer **71b** showed activity comparable with the activity of piperazine-based oximes.

Since the oxime series originated from the amide to methyleneoxime replacement (Chart 2), our SAR was focused on a two-methylene linker between the oxime group and a piperazine ring. In the final step of our SAR study, we evaluated the effect of the linker length and substitution. Comparison of the length of linker (Table 6) clearly confirmed that *E*-oximes, both free and *O*-methyl-substituted, with two-methylene linkers offered the highest efficacy when compared to one-or three-methylene linker analogues (**24a** and **58a** vs **73b**, **74b** vs **75a**, **76a**).

The one-methylene linker *E*-oxime **73a** (same orientation of *O*-methyl group as in *Z*-oximes with two- or three-methylene linkers) showed very low efficacy and $EC_{50} > 10$ μM, whereas the *Z*-isomer of three-methylene linker oxime **75b** was also a

Table 7. Evaluation of Linker Substitution





85a

compd	aryl$_1$	R$_1$	R$_2$	human D$_4$ FLIPR EC$_{50}$,^{a} nM	% E^b
77a	4-chlorophenyl	OH	Me	46 ± 1	89
77b	4-chlorophenyl	OH	Me	22.6 ± 0.3	94
78a	4-chlorophenyl	OMe	Me	195 ± 1	79
78b	4-chlorophenyl	OMe	Me	285 ± 1	83
79a	3-methylphenyl	OH	H	44.8 ± 0.5	66
79b	3-methylphenyl	OH	H	4.9 ± 2.3	81
80a	3-methylphenyl	OMe	H	5370 ± 1200	53
80b	3-methylphenyl	OMe	H	34.5 ± 0.6	69
81ab^c	4-chlorophenyl	Me	Me	459 ± 26	62
82a	4-chlorophenyl	CH_2NHOCH_3	Me	206 ± 41	93
83a	4-chlorophenyl	$CH_2OCH(CH_3)_2$	Me	3210 ± 120	60
84ab^d	3-pyridyl	OH	Me	123	80
85a			Et	4760 ± 370	40

^{a} Mean values for agonists (SEM, $n \geq 3$). ^{b} Efficacy relative to 10 μM dopamine (100%). ^{c} 3:1 mixture of *E*:*Z* isomers. ^{d} 2:1 mixture of *Z*:*E* isomers.

good D_4 agonist. On the other hand, the *Z*-one-methylene linker analogue **73b** showed potency comparable to its *E*-two-methylene linker (**24a**) and three-methylene linker (**75a**) counterparts, although the efficacy was significantly lower. The *E*-*O*-methyl analogue **74a** had low potency (EC$_{50}$ = 4.29 μM) and efficacy of 26% in comparison to the same stereo-related *Z*-isomers of two- and three-methylene linker analogues, **58b** and **76b**, respectively. The *Z*-isomer **74b** showed potency and efficacy almost as good as two-methylene linker compound **58a**). The three-methylene linker O-methylated analogues had almost the same potency and efficacy regardless of *Z* or *E* stereochemistry, and in addition **76b** showed D_2 agonist activity in FLIPR (EC$_{50}$ = 366 nM and % E = 65). In conclusion, the two-methylene linker was confirmed to be the most optimal linker for further evaluation.

Evaluation of substitution of the two-methylene linker was the final step of optimization (see Table 7). The substitution of α-carbon of the linker of *Z*-oxime (equivalent to the *E*-isomer with unsubstituted linker) with a hydrogen donor, like hydroxy or amino groups, preserved or even slightly improved the efficacy of compounds (for example, **77b** and **82a** vs **59a** or **79b** vs **22a**). Protection of hydroxy group and eliminating the possible internal hydrogen bonding resulted in lower potency as well as efficacy (for example, **78a** vs **77a** and **78b** vs **77b**, or **80a** vs **79a** and **80b** vs **79b**). The other non-hydrogen donor substituents also caused a loss of both potency and efficacy (**81ab**, **83a** vs **59a**), confirming that hydrogen donors in α-position might stabilize the more active oxime conformation by internal hydrogen bonding. The α-hydroxy analogue of aryl$_1$ 3-pyridine **84ab**, however, showed almost 4-fold loss of potency comparing to the deshydroxy analogue **68ab**, even if the efficacy was preserved. Connecting the α-substituent to the phenyl ring to form 3,4-dihydro-2*H*-naphthalen-1-one analogue **85a** led to dramatic loss of potency and efficacy (EC$_{50}$ = 4760 nM and % E = 40). More SAR studies in substitution of both α- and β-carbons of the linker, as well as separation of chiral isomers, are necessary to fully evaluate the effect of linker substitution on the selectivity and activity of oxime-based D_4 agonists.

Table 8. Binding Data for Selected Compounds

compd	D$_{4.4}$, K_i,^{a} nM	D$_{2L}$, K_i,^{b} nM	D$_2$/D$_4$
17a	25.4 ± 2	257 ± 16	10.3
31a	22.8 ± 6.7	172 ± 76	7.5
32a	38 ± 9	128 ± 55	3.3
37a	88 ± 16	140 ± 27	1.6
51a	168 ± 18	257 ± 4	1.5
53a	11.4 ± 1.8	112 ± 9	10
54a	13.9 ± 1.4	101 ± 5	7.5
54b	6.4 ± 0.2	46.6 ± 4.5	18
55a	13.5 ± 3.1	98.7 ± 7.4	7.3
56a	8 ± 1.6	68.4 ± 4.9	8.5
56b	32.1 ± 8.0	68.0 ± 5.3	2.1
57b	20.1 ± 1.1	125 ± 20.6	3.6
58a	14.2 ± 2.8	168 ± 40	3.8
58b	53.3 ± 5.8	221 ± 17.3	4.2
59a	38.2 ± 8.8	63.8 ± 26.2	1.7
61a	110 ± 33	132 ± 8	1.2
61b	6.3 ± 1	225 ± 34	36
64a	71.2 ± 11.9	171 ± 29.3	2.4
65a	6.4 ± 1.7	64.5 ± 11.6	11
66b	11.6 ± 3.7	60.9 ± 2.1	5
67a	27.5 ± 3.7	137 ± 20.3	4.9
68ab	130 ± 7	1820 ± 320	14.8
69a	67.1 ± 8.8	76.5 ± 7.9	1.1
70a	134 ± 17	25.3 ± 1.8	0.2
70b	90 ± 8.8	19.4 ± 1.4	0.2
74b	2050 ± 40	2530 ± 170	1.2
77a	113 ± 11	995 ± 170	8.8
77b	150 ± 14	368 ± 55	2.5
81ab	346 ± 13	146 ± 21	0.4
82a	120 ± 11	164 ± 18	1.4

^{a} Mean values for binding affinity with D_4-selective agonist radioligand [^{3}H]-A-369508[40] (SEM, $n \geq 4$). ^{b} Mean values for binding affinity with D_2-like agonist radioligand [^{125}I]-PIPAT (SEM, $n \geq 4$).

Compounds were tested for D_2 functional agonist activity to determine functional D_2/D_4 subtype selectivity, since the D_2 agonist activity was associated with the emetic effects of apomorphine.[14,15] Coexpression of D_{2L} receptor with chimeric Gα_{qo5} in HEK-293 cells allowed determination of functional selectivity against D_{2L} receptor and in identifying both agonists and antagonists.[39] None of the tested compounds showed D_2 agonist (EC$_{50}$ > 10 μM) or antagonist (IC$_{50}$ > 10 μM) activities in this assay.

Since tested compounds showed no functional D_2 agonist activity and no functional D_2 antagonist activity, the selected compounds were also further evaluated in D_4 and D_2 binding assays to further define D_2/D_4 selectivity. D_2-like agonist radioligand [^{125}I]-PIPAT was utilized to determine binding affinity for selected oxime-based agonists at human D_{2L} receptor. The results are shown in Table 8. The fact that compounds have affinity for D_{2L} receptor but showed no efficacy is not new. Kenakin and Onaran[46] already discussed this lack of correlation between affinity and efficacy.

As seen in Table 9, only a few analogues, **17a**, **53a**, **54b**, **61b**, and **68ab**, showed good D_2/D_4 selectivity based on binding affinities. In general, the series showed modest binding selectivity over D_2 receptor. Compounds with the 4-piperidine core (**70a,b**) were less selective on the basis of the D_2 binding assay.

A number of compounds with good D_4 activity in FLIPR were selected for in vivo testing in a rat penile erection model. In this model,[47] rats (n = 8−30) are observed over a 60 min period with and without the drug, and the number of incidence of erections is reported. The results are reported in Table 9. The compounds **59a** and **64a** showed the most robust activity in rat penile erection model. The compounds were as effective as the most efficacious dose of apomorphine (0.1 μmol/kg), and **59a** was 3 times more potent than apomorphine in this model.

Table 9. In Vivo Proerectile Activity of Selected Oximes[a]

compd	dose giving max. efficacy, μmol/kg	max. incidence of erections in rat, %
apomorphine	0.1	85
2	0.3	79
17a	0.3	60
31a	0.1	77
32a	0.3	55
58a	0.3	50
59a	0.03	85
61a	0.1	68
64a	1.0	85
65a	0.3	76
67a	0.1	68
74b	0.3	77

[a] The compounds were administered subcutaneously.

Table 10. Pharmacokinetic Profiles of **59a**, **64a**, and **17a**

		rat			dog		
compd	dose,[a] 1 mg/kg	V_β, L/kg	$T_{1/2}$, h	F, %	V_β, L/kg	$T_{1/2}$, h	F, %
59a	sc	4.3	1.9	94.8	4.8		
59a	po		2.3	16.3		6.2	39.8
64a	sc	8.2	nt[b]	nt	3.8		
64a	po		UC	18.6		6.1	42.9
17a	sc	1.0	0.8	68.1	1.8		
17a	po		UC	0.0		UC	0.0

[a] Compound was administered subcutaneously (sc) or orally (po). [b] Not tested.

Clozapine [3 μmol/kg, administered intraperitoneally (ip)] and haloperidol (1 μmol/kg, ip) blocked the erectogenic effect of **59a** but domperidone (10 μmol/kg, ip) did not. These data indicate that the effect is mediated via central dopaminergic mechanism, since the peripheral dopamine antagonist domperidone did not block the proerectile effect of **59a**.

The most potent compounds in vivo were further evaluated in rat and dog to determine pharmacokinetic profiles (Table 10). Compounds **59a** and **64a** were found to be orally bioavailable in rat and dog after 1 mg/kg dose. Compound **59a** showed $F =$ 16.3% and $T_{1/2} > 2$ h in rat and $F = 39.8\%$ and $T_{1/2} > 6$ h in dog, whereas **64a** showed $F = 18.6\%$ in rat and $F = 42.9\%$ with $T_{1/2}$ in dog the same as for **59a**. Both *O*-alkyloximes were characterized by high volumes of distribution values: $V_\beta = 4.3$ and 8.2 L/kg for **59a** and **64a**, respectively in rat and $V_\beta = 4.8$ L/kg for **59a** and 3.8 L/kg for **64a**, respectively, in dog. For comparison, the V_β value of oxime **17a** was only 1.0 L/kg in rat and 1.8 L/kg in dog. The higher volumes of distribution of **59a** and **64a** than **17a** are reflected in the longer elimination half-lives of *O*-methyloximes. In conclusion of pharmacokinetic studies, *O*-alkyloximes showed good oral bioavailability (~40%) and good half-life ($T_{1/2} > 6$ h) in dog.

Compound **59a**, a representative of the oxime series, was evaluated for cardiovascular and CNS effects. Compound **59a** was administered in anesthetized rats and achieved over 750 times the estimated efficacious plasma concentration (1.6 ng/mL in rat PE model) without any sustained dose-related effects on mean arterial pressure, heart rate, or hindquarters vascular resistance. Compound **59a** showed 14.7% prolongation of canine cardiac Purkinje fiber repolarization at 100 times the efficacious plasma level.

No CNS side effects were observed in mouse Irvin test up to 10 μmol/kg (>2000 times the efficacious dose). Low hypoactivity, piloerection, ptosis, and hypothermia were observed at 10 μmol/kg.

Since D_2 agonism was associated with the emetic activity of apomorphine, ferrets were used to evaluate the emetic potential of oxime series. The representative compound **59a** did not elicit emesis in ferrets at any tested dose (0.03−3 μmol/kg after subcutaneous administration), confirming the lack of agonist activity at D_2 receptors.

Conclusion

In conclusion, we demonstrated a successful introduction of a methyleneoxime functionality that led to a novel class of dopamine D_4 receptor agonists. These compounds showed very good agonist potencies and high efficacies at D_4 receptor. Among all of the 4-arylpiperazines tested, the highest potency and efficacy was observed for 4-pyridin-2-yl-piperazine analogues. The 1,4-disubstituted piperazine analogues and two-methylene linker between oxime and piperazine provided the most potent and efficacious agonists. Selected compounds showed good pharmacokinetics and good in vivo activity in the rat penile erection model. Consequently, **59a** and oxime series represent an exciting lead for developing the next generation of dopamine D_4 receptor agonists, potentially useful in treatment of erectile dysfunction and other CNS indications.

Experimental Section

Chemistry General. Melting points were taken on a Thomas−Hoover melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Nicolet QE-300 (300 MHz) instrument with Me_4Si (TMS) as the internal standard; chemical shifts are expressed in parts per million (ppm) relative to TMS in δ units. Mass spectra were obtained with a Hewlett-Packard HP5985 or Finnigan SSQ7000 spectrometer by use of different techniques such as desorption chemical ionization (DCI), electrospray ionization (ESI), or atmospheric pressure chemical ionization (APCI) as specified for individual compounds. X-ray crystallography was taken on a PS4 Siemens apparatus with CCD detector. Microanalyses were performed by the Robertson Microlit Laboratories, Inc., Madison, NJ. Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification.

N-Arylpiperazines were commercially available except for 3-methyl-1-(pyridin-2-yl)piperazine, the synthesis of which will be described.

General Procedure for Preparation of 1-Aryl-3-(4-arylpiperazin-1-yl)propan-1-one Oximes or *O*-Alkyloximes: Method A. 1-Aryl-3-(4-arylpiperazin-1-yl)-1-ethanone analogues were prepared as described in the literature.[31] To a mixture of *N*-arylpiperazine (7 mmol), 1-arylethanone (10 mmol), and paraformaldehyde (10 mmol) in 2-propanol (20 mL) was added slowly concentrated HCl (23 mmol) through the top of the condenser, and the resulting reaction mixture was refluxed for 12−24 h. The reaction was cooled and concentrated under reduced pressure, and the residue was treated carefully with saturated solution of $NaHCO_3$. It was then extracted with ethyl acetate, washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The oily residue was passed through a short pad of silica gel, with ethyl acetate as eluent to afford a roughly purified ketone, which was used directly to the next step.

Crude 1-aryl-3-(4-arylpiperazin-1-yl)propan-1-one (~1 mmol) was dissolved in pyridine (10 mL) and treated with hydroxylamine hydrochloride (2 mmol) or *O*-alkylhydroxylamine hydrochloride for 12 h at ambient temperature. The reaction mixture was concentrated under reduced pressure, and the residue was treated with saturated solution of $NaHCO_3$ and extracted with ethyl acetate. The acetate layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography with ethyl acetate as eluent for free oximes and methylene chloride/acetone 4:1 in the case of *O*-alkyloximes to provide the desired compounds.

General Procedure for Preparation of 1-Aryl-3-(4-arylpiperazin-1-yl)propan-1-one *O*-Alkyloximes: Method B. Crude 1-Aryl-

3-(4-arylpiperazin-1-yl)propan-1-one oxime (1 mmol) was dissolved in *tert*-butyl alcohol (15 mL) and treated with powdered potassium *t*-butoxide (1 mmol). The mixture was refluxed for ~30 min until the solution became clear. It was then cooled to ambient temperature, alkyl halide (1 mmol) was added, and the new mixture was refluxed for an additional 1 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (silica gel, 4:1 methylene chloride/acetone as eluent) to provide the desired *O*-alkyloximes.

General Procedure for Preparation of 1-Aryl-3-(4-arylpiperazin-1-yl)propan-1-one Oximes or *O*-Alkyloximes from 3-Aryl-1-chloro-3-propanones: Method C. A mixture of 1-aryl-3-chloro-1-propanones (5 mmol) and *N*-arylpiperazine (10 mmol) in toluene (35 mL) was refluxed for 8–16 h. The reaction was cooled to ambient temperature, and the solid was filtered off and washed with toluene. The filtrate and washings were combined and concentrated under reduced pressure. The residue was treated with hydroxylamine hydrochloride (10 mmol) or *O*-alkylhydroxylamine hydrochloride (10 mmol) in pyridine (25 mL) for 12–16 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography.

Method D. *N*-Arylpiperazine (10 mmol), 1-aryl-3-chloro-1-propanones (10 mmol), and anhydrous potassium carbonate (10 mmol) were combined in DMF (25 mL), and the resulting mixture was heated at 40 °C for 14 h. It was then poured into water and extracted with ethyl acetate. The acetate extract was washed with water and with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was treated with hydroxylamine hydrochloride (10 mmol) or *O*-alkylhydroxylamine (10 mmol) as described for method C.

(*E*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one Oxime (22a). Compound was prepared from 1-(*m*-tolyl)-ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by ethod A in 64% overall yield: mp 146–147 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.33 (s, 3H), 2.50 (m, 6H), 2.92 (m, 2H), 3.45 (t, J = 6 Hz, 4H), 6.62 (dd, J = 7 and 4.5 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.18 (d, J = 6 Hz, 1H), 7.28 (t, J = 7 Hz, 1H), 7.48 (m, 3H), 8.10 (dd, J = 4.5 Hz, 3 Hz, 1H); MS (DCI/NH_3) *m/z* 325 (M + H)$^+$. Anal. Calcd ($C_{19}H_{24}N_4O{\cdot}0.1H_2O$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (17a) and (*Z*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one Oxime (17b). Compounds were prepared from 3-chloro-1-phenylpropan-1-one, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method D in 55% and 10% overall yield, respectively. *E*-isomer: mp 169–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.95 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6,80 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.39 (m, 3H), 7.51 (m, 1H), 7.65 (m, 2H), 8.10 (m, 1H), 11.13 (s, 1H); MS (DCI/NH_3) *m/z* 311 (M + H)$^+$. Anal. Calcd ($C_{18}H_{22}N_4O{\cdot}0.25H_2O$): C, H, N. *Z*-isomer: mp 130–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (m, 4H), 2.70 (t, J = 7 Hz, 2H), 3.35 (m, 2H), 3.42 (m, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6,79 (d, J = 9 Hz, 1H), 7.40 (m, 6H), 8.09 (m, 1H), 10.58 (s, 1H); MS (DCI/NH_3) *m/z* 311 (M + H)$^+$.

(*E*)-1-(2-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (18a) and (*Z*)-1-(2-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (18b). Compounds were prepared from 1-(2-chlorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in 43% and 15% overall yield, respectively. **18a**: mp 161–162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, J = 4 Hz, 4H), 2.40 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 3.35 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 7.39 (m, 3H), 7.49 (m, 2H), 8.08 (m, 1H), 11.26 (s, 1H); MS (ESI+) *m/z* 345 (M + H)$^+$; MS (ESI−) *m/z* 343 (M − H)$^-$. Anal. Calcd ($C_{18}H_{21}ClN_4O{\cdot}0.15H_2O$): C, H, N. **18b**: mp 155–157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (t, J = 4 Hz, 6H), 2.64 (t, J = 7 Hz, 2H), 3.40 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 7.25 (m, 1H), 7.34 (m, 2H), 7.48 (m, 2H), 8.08 (m, 1H), 10.65 (s, 1H); MS (ESI+) *m/z* 345 (M + H)$^+$; MS (ESI−) *m/z* 343 (M−H)$^-$. Anal. Calcd ($C_{18}H_{21}ClN_4O$): C, H; N calcd 16.25, found 17.75.

(*E*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*o*-tolyl)propan-1-one Oxime (19a) and (*Z*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*o*-tolyl)-propan-1-one Oxime (19b). Compounds were prepared from 1-(*o*-tolyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in 49% and 16% overall yield, respectively. **19a**: mp 108–110 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.38 (m, 6H), 2.86 (t, J = 7 Hz, 2H), 3.37 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 7.22 (m, 6H), 7.49 (m, 1H), 8.08 (m, 1H), 11.00 (s, 1H); MS (ESI+) *m/z* 325 (M + H)$^+$; MS (ESI$^-$) *m/z* 323 (M − H)$^-$. Anal. Calcd ($C_{19}H_{24}N_4O$): C, H, N. **19b**: mp 128–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 2.40 (m, 6H), 2.64 (t, J = 7 Hz, 2H), 3.40 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 7.10 (m, 1H), 7.20 (m, 3H), 7.50 (m, 1H), 8.08 (m, 1H), 10.48 (s, 1H); MS (ESI+) *m/z* 325 (M + H)$^+$; MS (ESI−) *m/z* 323 (M − H)$^-$. Anal. Calcd ($C_{19}H_{24}N_4O$): C, H, N.

(*E*)-1-(3-Fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (20a). Compound was prepared from 1-(3-fluorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in overall 45% yield: mp 152–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.94 (m, 2H), 3.22 (t, J = 4 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.20 (m, 1H), 7.46 (m, 4H), 8.09 (m, 1H), 11.42 (s, 1H); MS (ESI+) *m/z* 329 (M + H)$^+$; MS (ESI−) *m/z* 327 (M − H)$^-$. Anal. Calcd ($C_{18}H_{21}FN_4O{\cdot}0.25H_2O$): C, H, N.

(*E*)-1-(3-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (21a). Compound was prepared from 1-(3-chlorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in overall 42% yield: mp 139–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.94 (m, 2H), 3.22 (t, J = 4 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.43 (m, 2H), 7.50 (m, 1H), 7.60 (m, 1H), 7.67 (m, 1H), 8.10 (m, 1H), 11.44 (s, 1H); MS (ESI+) *m/z* 345 (M + H)$^+$; MS (ESI−) *m/z* 343 (M − H)$^-$. Anal. Calcd ($C_{18}H_{21}ClN_4O$): C, H, N.

3-[1-Hydroxyimino-3-(4-pyridin-2-ylpiperazin-1-yl)propyl]-benzonitrile (23a). Compound was prepared from 3-acetylbenzonitrile, 1-pyrid-2-ylpiperazine, and hydroxylamine hydrochloride by method A in overall 20% yield: mp 147–149 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (m, 6H), 2.96 (t, J = 7 Hz, 2H), 3.22 (t, J = 4 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.46 (m, 1H), 7.60 (t, J = 7 Hz, 1H), 7.82 (m, 1H), 8.00 (m, 1H), 8.09 (m, 2H), 11.60 (s, 1H); MS (ESI+) *m/z* 336 (M + H)$^+$; MS (ESI−) *m/z* 334 (M − H)$^-$. Anal. Calcd ($C_{19}H_{21}N_5O{\cdot}0.2EtOAc$): C, H, N.

(*E*)-1-(4-Fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (24a). Compound was prepared from 3-chloro-1-(4-fluorophenyl)-1-propanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method D in overall 57% yield: mp 159–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.93 (m, 2H), 3.43 (t, J = 4.5 Hz, 4H), 6.61 (dd, J = 9 and 6 Hz, 1H), 7.80 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.51 (m, 1H), 7.70 (m, 2H), 8.10 (m, 1H), 11.26 (s, 1H); MS (DCI/NH_3) *m/z* 329 (M + H)$^+$. Anal. Calcd ($C_{18}H_{21}FN_4O{\cdot}0.5H_2O$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (25a). Compound was prepared from 3-chloro-1-(4-chlorophenyl)propan-1-one, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method C in overall 61% yield: mp 188–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.93 (m, 2H), 3.43 (t, J = 4.5 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.50 (m, 3H), 7.66 (m, 2H), 8.10 (m, 1H), 11.38 (s, 1H); MS (DCI/NH_3) *m/z* 345 (M + H)$^+$. Anal. Calcd ($C_{18}H_{21}ClN_4O$): C, H, N.

(*E*)-1-(3,5-Difluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one Oxime (26a) and (*Z*)-1-(3,5-Difluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (26b). Compounds were prepared from 1-(3,5-difluorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in

overall 38% and 5% yield, respectively. **26a**: mp 150–151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.95 (t, J = 7 Hz, 2H), 3.24 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.25 (m, 1H), 7.34 (m, 2H), 7.46 (m, 1H), 8.09 (m, 1H), 11.60 (s, 1H); MS (ESI+) m/z 347 (M + H)$^+$; MS (ESI−) m/z 345 (M − H)$^-$. Anal. Calcd ($C_{18}H_{20}F_2N_4O$): C, H, N. **26b**: mp 123–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (m, 4H), 2.50 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 3.42 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.20 (m, 3H), 7.50 (m, 1H), 8.09 (m, 1H), 10.90 (s, 1H); MS (ESI+) m/z 347 (M + H)$^+$; MS (ESI−) m/z 345 (M − H)$^-$.

(*E*)-1-(3,5-Dimethylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one Oxime (27a). Compound was prepared from 1-(3,5-dimethylphenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in overall 67% yield: mp 127–128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 6H), 2.50 (m, 6H), 2.95 (m, 2H), 3.24 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.00 (m, 1H), 7.24 (m, 2H), 7.46 (m, 1H), 8.09 (m, 1H), 11.12 (s, 1H); MS (ESI+) m/z 339 (M + H)$^+$; MS (ESI−) m/z 337 (M − H)$^-$. Anal. Calcd ($C_{20}H_{26}N_4O$): C, H, N.

(*E*)-1-(2,4-Difluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one Oxime (28a). Compound was prepared from 1-(2,4-difluorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in overall 23% yield: mp 115–117 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (m, 6H), 2.93 (t, J = 7 Hz, 2H), 3.32 (m, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.78 (d, J = 7 Hz, 1H), 7.10 (m, 1H), 7.27 (m, 1H), 7.50 (m, 2H), 8.07 (m, 1H), 11.40 (s, 1H); MS (ESI+) m/z 347 (M + H)$^+$; MS (ESI−) m/z 345 (M − H)$^-$.

(*E*)-1-(2-Benzyloxy-5-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (29a) and (*Z*)-1-(2-Benzyloxy-5-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (29b). Compounds were prepared from 1-(2-benzyloxy-5-methylphenyl)ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method A in 61% and 12% overall yield, respectively. **29a**: mp 176–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.28 (t, J = 4 Hz, 4H), 2.37 (t, J = 7 Hz, 2H), 2.81 (t, J = 7 Hz, 2H), 3.35 (t, J = 4 Hz, 4H), 5.21 (s, 2H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 7.01 (m, 2H), 7.12 (m, 1H), 7.40 (m, 5H), 7.50 (m, 1H), 8.10 (m, 1H), 10.94 (s, 1H); MS (ESI+) m/z 431 (M + H)$^+$; MS (ESI−) m/z 429 (M − H)$^-$. Anal. Calcd ($C_{26}H_{30}N_4O_2$): C, H, N. **29b**: mp 149–152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.38 (m, 6H), 2.60 (t, J = 7 Hz, 2H), 3.40 (t, J = 4 Hz, 4H), 5.05 (s, 2H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 6.92 (m, 1H), 7.00 (m, 1H), 7.08 (m, 1H), 7.38 (m, 5H), 7.50 (m, 1H), 8.08 (m, 1H), 10.38 (s, 1H); MS (ESI+) m/z 431 (M + H)$^+$; MS (ESI−) m/z 429 (M − H)$^-$.

(*E*)-1-(2-Hydroxy-5-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one Oxime (30a). (*E*)-1-(2-Benzyloxy-5-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime (86 mg, 0.2 mmol) was treated with 33% HBr/AcOH at room temperature for 4 h. The mixture was then concentrated under reduced pressure and the residue was treated with saturated $NaHCO_3$. The product was extracted with EtOAc and dried over anhydrous $MgSO_4$. Concentration under reduced pressure and chromatography (EtOAc as eluent) provided 25 mg (37%) of product: mp 157–158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.55 (m, 6H), 3.00 (t, J = 7 Hz, 2H), 3.46 (t, J = 4 Hz, 4H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 6.82 (d, J = 7 Hz, 1H), 7.03 (m, 1H), 7.25 (m, 1H), 7.50 (m, 1H), 8.10 (m, 1H), 11.01 (s, 1H), 11.50 (s, 1H); MS (ESI+) m/z 341 (M + H)$^+$; MS (ESI−) m/z 339 (M − H)$^-$. Anal. Calcd ($C_{19}H_{24}N_4O_2$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (31a) and (*Z*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (31b). Compounds were prepared from 3-chloro-1-phenylpropan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method D in 47% and 19% overall yield, respectively. **31a** maleate salt: mp 142–144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m, 12H), 3.98 (s, 3H), 6.08 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.45 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 325 (M + H)$^+$. Anal. Calcd ($C_{19}H_{24}N_4O \cdot C_4H_4O_4$): C, H, N. **31b** maleate salt: mp 96–98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.97 (m, 2H), 3.30 (m, 10H), 3.79 (s, 3H), 6.08 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.45 (m, 5H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 325 (M + H)$^+$. Anal. Calcd ($C_{19}H_{24}N_4O \cdot C_4H_4O_4 \cdot 0.25H_2O$): C, H, N.

***E*-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Ethyloxime (32a) and *Z*-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Ethyloxime (32b).** Compounds were prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and iodoethane by method B in 43% and 4% overall yield, respectively. **32a** maleate salt: mp 150–151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (t, J = 7 Hz, 3H), 3.25 (m, 12H), 4.21 (t, J = 7 Hz, 2H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 339 (M + H)$^+$. Anal. Calcd ($C_{20}H_{26}N_4O \cdot C_4H_4O_4$): C, H, N. **32b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (t, J = 7 Hz, 3H), 2.41 (m, 6H), 2.70 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.99 (t, J = 7 Hz, 2H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.40 (m, 5H), 7.70 (m, 1H), 8.09 (m, 1H); MS (DCI/NH_3) m/z 339 (M + H)$^+$.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Propyloxime (33a). Compound was prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and 1-iodopropane by method B in 48% overall yield: maleate salt, mp 153–154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, J = 7 Hz, 3H), 1.71 (sextet, J = 7 Hz, 2H), 3.25 (m, 12H), 4.18 (t, J = 7 Hz, 2H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O \cdot C_4H_4O_4$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Butyloxime (34a). Compound was prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and 1-iodobutane by method B in 27% overall yield: maleate salt, mp 154–155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, J = 7 Hz, 3H), 1.40 (sextet, J = 7 Hz, 2H), 1.68 (q, J = 7 Hz, 2H), 3.25 (m, 12H), 4.18 (t, J = 7 Hz, 2H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 367 (M + H)$^+$. Anal. Calcd ($C_{22}H_{30}N_4O \cdot C_4H_4O_4 \cdot 0.4H_2O$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Isopropyloxime (35a). Compound was prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and 2-iodopropane by method B in 52% overall yield: maleate salt, mp 156–157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, J = 7 Hz, 6H), 3.25 (m, 12H), 4.42 (q, J = 7 Hz, 1H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O \cdot C_4H_4O_4 \cdot 0.6H_2O$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Allyloxime (36a). Compound was prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and 3-bromopropene by method B in 51% overall yield: maleate salt, mp 136–137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (m, 12H), 4.70 (m, 2H), 5.30 (m, 2H), 6.07 (s + m, 3.4H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.60 (m, 1H), 7.70 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 351 (M + H)$^+$. Anal. Calcd ($C_{21}H_{26}N_4O \cdot 1.2C_4H_4O_4$): C, H, N.

[1-Phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propylideneaminooxy]-acetonitrile (37a). Compound was prepared from a crude 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one oxime and bromoacetonitrile by method B in 36% overall yield: maleate salt, mp 127–128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 5.13 (s, 2H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.50 (m, 3H), 7.60 (m, 1H), 7.73 (m, 2H), 8.16 (m, 1H);

MS (DCI/NH_3) *m/z* 350 (M + H)$^+$. Anal. Calcd ($C_{20}H_{23}N_5O{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-2-[4-(3-Hydroxyimino-3-phenylpropyl)piperazin-1-yl]nicotinonitrile (38a) and (*Z*)-2-[4-(3-Hydroxyimino-3-phenylpropyl)piperazin-1-yl]nicotinonitrile (38b). Compounds were prepared from 3-chloro-1-phenylpropan-1-one, 2-piperazin-1-ylnicotinonitrile, and hydroxylamine hydrochloride by method D in 66% and 8% overall yield, respectively. 38a: mp 168–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 2H), 2.57 (t, J = 4.5 Hz, 4H), 2.94 (m, 2H), 3.58 (t, J = 4.5 Hz, 4H), 6.91 (dd, J = 7.5 and 4.8 Hz, 1H), 7.37 (m, 3H), 7.64 (m, 2H), 8.05 (dd, J = 7.5 and 2.0 Hz, 1H), 8.40 (dd, J = 4.8 and 2.0 Hz, 1H); MS (DCI/NH_3) *m/z* 336 (M + H)$^+$. Anal. Calcd ($C_{19}H_{21}N_5O$): C, H, N. 38b: mp 169–171 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.46 (m, 6H), 2.69 (t, J = 7 Hz, 2H), 3.56 (t, J = 4.5 Hz, 4H), 6.91 (dd, J = 7.5 and 4.8 Hz, 1H), 7.39 (m, 5H), 8.05 (dd, J = 7.5 and 2.0 Hz, 1H), 8.39 (dd, J = 4.8 and 2.0 Hz, 1H); MS (DCI/NH_3) *m/z* 336 (M + H)$^+$. Anal. Calcd ($C_{19}H_{21}N_5O{\cdot}0.20H_2O$): C, H, N.

(*E*)-1-Phenyl-3-(4-pyrimidin-2-ylpiperazin-1-yl)propan-1-one Oxime (39a) and (*Z*)-1-Phenyl-3-(4-pyrimidin-2-ylpiperazin-1-yl)propan-1-one Oxime (39b). Compounds were prepared from 3-chloro-1-phenylpropan-1-one, 2-piperazin-1-ylpyrimidine, and hydroxylamine hydrochloride by method D in 44% and 4% overall yield, respectively. **39a**: mp 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 6H), 2.95 (m, 2H), 3.70 (t, J = 4.5 Hz, 4H), 6.61 (t, J = 4.5 Hz, 1H), 7.39 (m, 3H), 7.64 (m, 2H), 8.33 (d, J = 4.5 Hz, 1H), 11.23 (s, 1H); MS (DCI/NH_3) *m/z* 312 (M + H)$^+$. Anal. Calcd ($C_{17}H_{21}N_5O{\cdot}0.15H_2O$): C, H; N calcd 22.30, found 21.79. **39b**: mp 159–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (m, 6H), 2.69 (t, J = 7 Hz, 2H), 3.67 (t, J = 4.5 Hz, 4H), 6.60 (t, J = 4.5 Hz, 1H), 7.40 (m, 5H), 8.35 (d, J = 4.5 Hz, 1H), 10.58 (s, 1H); MS (DCI/NH_3) *m/z* 312 (M + H)$^+$.

(*E*)-1-Phenyl-3-(4-thiazol-2-ylpiperazin-1-yl)propan-1-one Oxime (40a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-thiazol-2-ylpiperazine, and hydroxylamine hydrochloride by method D in 49% overall yield: mp 153–155 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.22 (m, 4H), 2.63 (m, 4H), 3.12 (m, 2H), 4.05 (m, 2H), 6.70 (d, J = 3 Hz, 1H), 7.51 (d, J = 3 Hz, 1H), 7.35 (m, 3H), 7.70 (m, 2H). MS (DCI/NH_3) *m/z* 317 (M + H)$^+$. Anal. Calcd ($C_{16}H_{20}N_4OS$): C, H, N.

1-Phenyl-3-(4-phenylpiperazin-1-yl)propan-1-one *O*-Ethyloxime (41a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-phenylpiperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 39% overall yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 2.65 (m, 6H), 3.03 (m, 2H), 3.21 (m, 4H), 4.25 (q, J = 7 Hz, 2H), 6.85 (m, 1H), 6.95 (d, J = 7.5 Hz, 2H), 7.30 (m, 2H), 7.44 (m, 3H), 7.65 (m, 2H); MS (DCI/NH_3) *m/z* 338 (M + H)$^+$. **41a** maleate salt: mp 151–152 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7 Hz, 3H), 3.30 (m, 6H), 3.48 (m, 6H), 4.49 (q, J = 7 Hz, 2H), 6.24 (s, 2H), 6.92 (t, J = 7 Hz, 1H), 7.01 (d, J = 7 Hz, 2H), 7.28 (m, 2H), 7.42 (m, 3H), 7.70 (m, 2H). Anal. Calcd ($C_{21}H_{27}N_3O{\cdot}C_4H_4O_4$): C, H, N.

2-[4-(Ethoxyimino-3-phenylpropyl)piperazin-1-yl]benzonitrile (42a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 2-piperazin-1-ylbenzonitrile, and *O*-ethylhydroxylamine hydrochloride by method D in 37% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7 Hz, 3H), 2.75 (m, 6H), 3.04 (br s, 2H), 3.25 (br s, 4H), 4.25 (q, J = 7 Hz, 2H), 7.01 (m, 2H), 7.35 (m, 4H), 7.45 (m, 1H), 7.55 (dd, J = 9 Hz, 3 Hz, 1H), 7.70 (m, 2H); MS (DCI/NH_3) *m/z* 363 (M + H)$^+$. **42a** maleate salt: mp 125–126 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7 Hz, 3H), 3.30 (m, 6H), 3.50 (m, 6H), 4.31 (q, J = 7 Hz, 2H), 6.25 (s, 2H), 7.22 (m, 2H), 7.42 (m, 3H), 7.70 (m, 4H). Anal. Calcd ($C_{22}H_{26}N_4O{\cdot}C_4H_4O_4$): C, H, N.

3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-phenylpropan-1-one *O*-Ethyloxime (43a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-(2-methoxyphenyl)piperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 44% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3H), 2.74 (m, 6H), 3.1 (m, 6H), 3.82 (s, 3H), 4.25 (q, J = 7.5 Hz, 2H), 6.92 (m, 4H), 7.44 (m, 3H), 7.7 (m, 2H); MS (DCI/NH_3) *m/z* 368 (M + H)$^+$. **43a** maleate salt: mp 146–147 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7 Hz, 3H), 3.29 (m, 6H), 3.86 (s, 3H), 3.49 (m, 6H), 4.30 (q, J = 7 Hz, 2H), 6.25 (s, 2H), 7.00 (m, 4H), 7.42 (m, 3H), 7.71 (m, 2H). Anal. Calcd ($C_{22}H_{29}N_3O_2{\cdot}C_4H_4O_4$): C, H, N.

3-[4-(3-Methoxyphenyl)piperazin-1-yl]-1-phenylpropan-1-one *O*-Ethyloxime (44a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-(3-methoxyphenyl)piperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 30% overall yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.33 (t, J = 7.5 Hz, 3H), 2.53 (m, 6H), 2.92 (m, 2H), 3.10 (m, 4H), 3.65 (s, 3H), 4.24 (q, J = 7.5 Hz, 2H), 6.41 (m, 3H), 7.10 (t, J = 7 Hz, 1H), 7.42 (m, 3H), 7.65 (m, 2H); MS (DCI/NH_3) *m/z* 368 (M + H)$^+$. **44a** maleate salt: mp 148–149 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7 Hz, 3H), 3.30 (m, 6H), 3.48 (m, 6H), 3.77 (s, 3H), 4.30 (q, J = 7 Hz, 2H), 6.25 (s, 2H), 6.58 (m, 3H), 7.20 (t, J = 7 Hz, 1H), 7.43 (m, 3H), 7.72 (m, 2H). Anal. Calcd ($C_{22}H_{29}N_3O_2{\cdot}C_4H_4O_4$): C, H, N.

3-[4-(4-Methoxyphenyl)piperazin-1-yl]-1-phenylpropan-1-one *O*-Ethyloxime (45a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-(3-methoxyphenyl)piperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 25% overall yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (t, J = 7.5 Hz, 3H), 2.52 (m, 6H), 3.03 (m, 6H), 3.65 (s, 3H), 4.25 (q, J = 7.5 Hz, 2H), 6.83 (m, 4H), 7.41 (m, 3H), 7.62 (m, 2H); MS (DCI/NH_3) *m/z* 368 (M + H)$^+$. **45a** maleate salt: mp 129–131 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7 Hz, 3H), 3.30 (m, 6H), 3.38 (m, 3H), 3.52 (m, 3H), 3.75 (s, 3H), 4.30 (q, J = 7 Hz, 2H), 6.25 (s, 2.4H), 6.88 (d, J = 9 Hz, 2H), 7.00 (d, J = 9 Hz, 2H), 7.43 (m, 3H), 7.71 (m, 2H). Anal. Calcd ($C_{22}H_{29}N_3O_2{\cdot}1.2C_4H_4O_4{\cdot}0.3H_2O$): C, H, N.

3-[4-(2-Ethoxyphenyl)piperazin-1-yl]-1-phenylpropan-1-one *O*-Ethyloxime (46a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-(3-methoxyphenyl)piperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 23% overall yield: maleate salt, mp 108–109 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, J = 7 Hz, 3H), 1.35 (t, J = 7 Hz, 3H), 3.25 (m, 12H), 4.03 (q, J = 7 Hz, 2H), 4.23 (q, J = 7 Hz, 2H), 6.05 (s, 2H), 6.95 (m, 4H), 7.45 (m, 3H), 7.72 (m, 2H); MS (DCI/NH_3) *m/z* 382 (M + H)$^+$. Anal. Calcd ($C_{23}H_{31}N_3O_2{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-3-[4-(2-Isopropoxyphenyl)-piperazin-1-yl]-1-phenylpropan-1-one *O*-Ethyloxime (47a) and (*Z*)-3-[4-(2-Isopropoxyphenyl)piperazin-1-yl]-1-phenylpropan-1-one *O*-Methyloxime (47b). 2-Isopropoxyaniline (3.5 g, 23 mmol) was added slowly to bis(2-chloroethyl)amine hydrochloride in *n*-butanol and then refluxed for 48 h. The reaction mixture was cooled to ambient temperature, treated with anhydrous Na_2CO_3 (9 g, 85 mmol), and refluxed for the next 48 h. The mixture was diluted with dicholoromethane and treated with a solution of 3 N NaOH. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 2.3 g (63%) of crude 1-(2-isopropoxyphenyl)piperazine. MS (DCI/NH_3) *m/z* 221(M + H)$^+$.

The title compounds were prepared from 3-chloro-1-(4-fluorophenyl)propan-1-one, 1-(2-isopropoxyphenyl)piperazine, and *O*-methylhydroxylamine hydrochloride by method D in 14% and 5% overall yield, respectively. **47a** maleate salt: mp 141–143 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (d, J = 7 Hz, 6H), 3.25 (m, 12H), 3.97 (s, 3H), 4.61 (septet, J = 7 Hz, 1H), 6.05 (s, 2H), 6.93 (m, 4H), 7.30 (t, J = 9 Hz, 2H), 7.77 (dd, J = 9 and 4 Hz, 2H); MS (DCI/NH_3) *m/z* 400 (M + H)$^+$. Anal. Calcd ($C_{23}H_{30}FN_3O_2{\cdot}C_4H_4O_4$): C, H, N. **47b** maleate salt: mp 103–105 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.34 (d, J = 7 Hz, 6H), 3.30 (m, 9H), 3.48 (m, 3H), 4.03 (s, 3H), 4.63 (septet, J = 7 Hz, 1H), 6.05 (s, 2H), 6.99 (m, 4H), 7.18 (t, J = 9 Hz, 2H), 7.77 (dd, J = 9 and 4 Hz, 2H); MS (DCI/NH_3) *m/z* 400 (M + H)$^+$.

2-[4-(3-Ethoxyimino-3-phenylpropyl)piperazin-1-yl]nicotinonitrile (48a). Compound was prepared from 1-phenyl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one, 2-piperazin-1-ylnicotinonitrile, and *O*-ethylhydroxylamine by method D in 37% overall yield: maleate salt, mp 120–121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, J = 7 Hz, 3H), 3.25 (m, 12H), 4.21 (q, J = 7 Hz, 2H), 6.06 (s, 2H), 7.03 (m, 1H), 7.43 (dd, J = 6 and 3 Hz, 3H), 7.70 (m, 2H),

8.15 (m, 1H), 8.26 (m, 1H); MS (DCI/NH_3) *m/z* 364 (M + H)$^+$. Anal. Calcd ($C_{21}H_{25}N_5O{\cdot}C_4H_4O_4$): C, H, N.

3-[4-(3-Methylpyridin-2-yl)piperazin-1-yl]-1-phenylpropanon-1-one *O*-Ethyloxime (49a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-(3-methylpiperidin-2-yl)piperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 20% overall yield: maleate salt, mp 132–134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 3.25 (m, 12H), 4.23 (q, J = 7 Hz, 2H), 6.05 (s, 2H), 7.00 (dd, J = 9 and 4 Hz, 1H), 7.45 (m, 3H), 7.55 (m, 1H), 7.70 (m, 2H), 8.14 (m, 1H); MS (DCI/NH_3) *m/z* 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O{\cdot}C_4H_4O_4$): C, H, N.

1-Phenyl-3-(4-pyrimidin-2-ylpiperazin-1-yl)propanon-1-one *O*-Ethyloxime (50a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 2-piperazin-1-ylpyrimidine, and *O*-ethylhydroxylamine hydrochloride by method D in 40% overall yield: maleate salt, mp 147–148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 3.25 (m, 12H), 4.21 (q, J = 7 Hz, 2H), 6.07 (s, 2H), 6.73 (m, 1H), 7.44 (m, 3H), 7.68 (m, 2H), 8.42 (d, J = 6 Hz, 2H); MS (DCI/NH_3) *m/z* 340 (M + H)$^+$. Anal. Calcd ($C_{19}H_{25}N_5O{\cdot}C_4H_4O_4$): C, H, N.

1-Phenyl-3-(4-thiazol-2-ylpiperazin-1-yl)propanon-1-one *O*-Ethyloxime (51a). Compound was prepared from 3-chloro-1-phenylpropan-1-one, 1-thiazol-2-ylpiperazine, and *O*-ethylhydroxylamine hydrochloride by method D in 17% overall yield: maleate salt, mp 122–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (t, J = 7 Hz, 3H), 3.25 (m, 12H), 4.21 (q, J = 7 Hz, 2H), 6.07 (s, 2H), 6.95 (m, 1H), 7.22 (d, J = 3 Hz, 1H), 7.45 (m, 3H), 7.70 (m, 2H); MS (DCI/NH_3) *m/z* 345 (M + H)$^+$. Anal. Calcd ($C_{18}H_{24}N_4OS{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-1-(2-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (52a) and (*Z*)-1-(2-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (52b). Compounds were prepared from 1-(2-chlorophenyl)ethanone, 1(pyridin-2-yl)piperazine, and *O*-methylhydroxylamine hydrochloride by method A in 29% and 28% overall yields, respectively. **52a** maleate salt: mp 129–130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 3.93 (s, 3H), 6.09 (s, 2.8H), 6.72 (m, 1H), 6.90 (d, J = 9 Hz, 1H), 7.50 (m, 5H), 8.15 (m, 1H); MS (DCI/NH_3) *m/z* 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}1.4C_4H_4O_4$): C, H, N. **52b** maleate salt: mp 113–116 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 2.93 (m, 2H), 3.35 (m, 10H), 3.75 (s, 3H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.32 (m, 1H), 7.42 (m, 2H), 7.60 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}1.6C_4H_4O_4$): C, H, N.

(*E*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*o*-tolyl)propan-1-one *O*-Methyloxime (53a) and (*Z*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*o*-tolyl)propan-1-one *O*-Methyloxime (53b). Compounds were prepared from 1-(*o*-tolyl)ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 38% and 12% overall yields, respectively. **53a**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H), 2.46 (m, 4H), 2.91 (m, 2H), 3.30 (m, 2H), 3.42 (m, 4H), 3.90 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.21 (m, 1H), 7.30 (t, J = 7 Hz, 1H), 7.50 (m, 3H), 8.10 (m, 1H); MS (DCI/NH_3) *m/z* 339 (M + H)$^+$. Anal. Calcd ($C_{20}H_{26}N_4O$): C, H, N. **53b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H), 2.40 (m, 6H), 2.68 (t, J = 7 Hz, 2H), 3.21 (m, 4H), 3.70 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.18 (m, 3H), 7.28 (m, 1H), 7.50 (m, 1H), 8.10 (m, 1H); MS (DCI/NH_3) *m/z* 339 (M + H)$^+$. Anal. Calcd ($C_{20}H_{26}N_4O$): C, H, N.

(*E*)-1-(3-Fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (54a) and (*Z*)-1-(3-Fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (54b). Compounds were prepared from 1-(3-fluorophenyl)ethanone, 1-(pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 35% and 18% overall yields, respectively. **54a** maleate salt: mp 157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 3.98 (s, 3H), 6.08 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95(d, J = 9 Hz, 1H), 7.30 (m, 1H), 7.52 (m, 3H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 343 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}FN_4O{\cdot}C_4H_4O_4$): C, H, N. **54b** maleate salt: mp 122–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (m, 2H), 3.30 (m, 10H), 3.79 (s, 3H), 6.08 (s, 2.5H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.33 (m, 3H), 7.50 (m, 1H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 343 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}FN_4O{\cdot}1.25C_4H_4O_4{\cdot}0.4H_2O$): C, H, N.

(*E*)-1-(3-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (55a) and (*Z*)-1-(3-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (55b). Compounds were prepared from 1-(3-chlorophenyl)ethanone, 1-(pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 24% and 15% overall yields, respectively. **55a** maleate salt: mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.24 (m, 12H), 3.98 (s, 3H), 6.08 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.50 (m, 2H), 7.62 (m, 2H), 7.73 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}C_4H_4O_4$): C, H, N. **55b** maleate salt: mp 145–147 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 3.79 (s, 3H), 6.08 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.46 (m, 3H), 7.58 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}C_4H_4O_4{\cdot}0.4H_2O$): C, H, N.

(*E*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one *O*-Methyloxime (56a) and (*Z*)-3-(4-Pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one *O*-Methyloxime (56b). Compounds were prepared from 1-(*m*-tolyl)ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 34% and 24% overall yields, respectively. **56a** maleate salt: mp 124–125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 3.25 (m, 12H), 3.90 (s, 3H), 6.08 (s, 2H), 6.72 (dd, J = 7 and 4 Hz, 1H), 6.91 (d, J = 9 Hz, 1H), 7.28 (m, 4H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 339 (M + H)$^+$. Anal. Calcd ($C_{20}H_{26}N_4O{\cdot}C_4H_4O_4{\cdot}0.4H_2O$): C, H, N. **56b** maleate salt: mp 119–121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3H), 2.87 (m, 2H), 3.30 (m, 12H), 3.74 (s, 3H), 6.08 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.14 (m, 1H), 7.25 (m, 4H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 339 (M + H)$^+$. Anal. Calcd ($C_{20}H_{26}N_4O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$): C, H, N.

(*E*)-4-[1-Methoxyimino-3-(4-pyridin-2-ylpiperazin-1-yl)propyl]benzonitrile (57a) and (*Z*)-4-[1-Methoxyimino-3-(4-pyridin-2-ylpiperazin-1-yl)propyl]benzonitrile (57b). Compounds were prepared from 3-acetylbenzonitrile, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 25% and 13% overall yields, respectively. **57a** maleate salt: mp 161–163 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m, 12H), 4.00 (s, 3H), 6.08 (s, 2.8H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.96 (d, J = 9 Hz, 1H), 7.64 (m, 2H), 7.93 (m, 1H), 8.03 (m, 1H), 8.10 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 350 (M + H)$^+$. Anal. Calcd ($C_{20}H_{23}N_5O{\cdot}1.4C_4H_4O_4$): C, H, N. **57b**: mp 105–108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (m, 6H), 2.73 (t, J = 7 Hz, 2H), 3.40 (m, 4H), 3.73 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.50 (m, 1H), 7.62 (t, J = 9 Hz, 1H), 7.75 (m, 1H), 7.83 (m, 1H), 7.89 (m, 1H), 8.09 (m, 1H); MS (DCI/NH_3) *m/z* 350 (M + H)$^+$. Anal. Calcd ($C_{20}H_{23}N_5O$): C, H, N.

(*E*)-1-(4-Fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (58a) and (*Z*)-1-(4-fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (58b). Compounds were prepared from 1-(4-fluorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 31% and 7% overall yields, respectively. **58a** maleate salt: mp 157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m, 12H), 3.98 (s, 3H), 6.08 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.30 (m, 1H), 7.55 (m, 4H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 343 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}FN_4O{\cdot}C_4H_4O_4$): C, H, N. **58b** maleate salt: mp 122–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 3.80 (s, 3H), 6.08 (s, 2.5H), 6.75 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.34 (m, 3H), 7.50 (m, 1H), 7.61(m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 343 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}FN_4O{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (59a) and (*Z*)-1-(4-Chlorophenyl)-3-

(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (59b). Compounds were prepared from 3-chloro-1-(4-chlorophenyl)-propan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method C in 52% and 14% overall yields, respectively. **59a**: mp 67−68 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45 (m, 6H), 2.93 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.93 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.50 (m, 3H), 7.68 (m, 2H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 359 (M + H)$^+$. **59a** maleate salt: mp 164−165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m, 12H), 3.98 (s, 3H), 6.08 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.50 (m, 2H), 7.60 (m, 1H), 7.73 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}C_4H_4O_4$): C, H, N. **59b**: mp 61−64 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (m, 6H), 2.70 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.72 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.45 (m, 5H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 359 (M + H)$^+$. **59b** maleate salt: mp 150−151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 12H), 3.79 (s, 3H), 6.08 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.46 (m, 3H), 7.58 (m, 2H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 359 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O{\cdot}C_4H_4O_4{\cdot}0.4H_2O$): C, H, N.

(*E*)-1-(4-Bromophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (60a) and (*Z*)-1-(4-Bromophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (60b). Compounds were prepared from 1-(4-bromophenyl)ethanone, 1-(pyridin-2-yl)piperazine, and *O*-methylhydroxylamine hydrochloride by method A in 35% and 24% overall yields, respectively. **60a**: oil, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45 (m, 6H), 2.92 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.93 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.50 (m, 1H), 7.71 (s, 4H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 403 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}BrN_4O$): C, H, N. **60b**: oil, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (m, 6H), 2.70 (t, J = 7 Hz, 2H), 3.40 (t, J = 4.5 Hz, 4H), 3.70 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.39 (d, J = 9 Hz, 2H), 7.50 (m, 1H), 7.61 (d, J = 9 Hz, 2H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 403 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}BrN_4O$): C, H, N.

(*E*)-1-(3,5-Difluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one *O*-Methyloxime (61a) and (*Z*)-1-(3,5-Difluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (61b). Compounds were prepared from 1-(3,5-difluorophenyl)-ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 42% and 23% overall yields, respectively. **61a**: mp 70−73 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45 (m, 6H), 2.92 (t, J = 7 Hz, 2H), 3.40 (t, J = 4 Hz, 4H), 3.94 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.33 (m, 3H), 7.50 (m, 1H), 8.09 (m, 1H); MS (DCI/NH_3) m/z 361 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}F_2N_4O{\cdot}0.3H_2O$): C, H, N. **61b** maleate salt: mp 137−138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (m, 2H), 3.23 (m, 10H), 3.80 (s, 3H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.30 (m, 3H), 7.60 (m, 1H), 8.16 (m, 1H); (DCI/NH_3) m/z 361 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}F_2N_4O{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-1-(3,5-Dimethylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one *O*-Methyloxime (62a) and (*Z*)-1-(3,5-Dimethylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (62b). Compounds were prepared from 1-(3,5-dimethylphenyl)-ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 42% and 8% overall yields, respectively. **62a** maleate salt: mp 167−168 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 6H), 3.20 (m, 12H), 3.95 (s, 3H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.08 (m, 1H), 7.28 (m, 2H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O{\cdot}C_4H_4O_4{\cdot}0.6H_2O$): C, H, N. **62b** maleate salt: mp 131−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 6H), 2.96 (m, 2H), 3.30 (m, 10H), 3.77 (s, 3H), 6.07 (s, 3H), 6.75 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.08 (m, 3H), 7.28 (m, 2H), 7.60 (m, 1H), 8.16 (m, 1H); (DCI/NH_3) m/z 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O{\cdot}1.5C_4H_4O_4$): C, H, N.

(*E*)-1-(2,4-Dichlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one *O*-Methyloxime (63a) and (*Z*)-1-(2,4-Dichlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (63b). Compounds were prepared from 1-(2,4-dichlorophenyl)-ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 14% and 20% overall yields, respectively. **63a**: oil, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.45 (m, 6H), 2.92 (t, J = 7 Hz, 2H), 3.37 (m, 4H), 3.90 (s, 3H), 6.61 (m, 1H), 6.78 (d, J = 9 Hz, 1H), 7.50 (m, 3H), 7.71 (s, 1H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 393 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}Cl_2N_4O{\cdot}0.25H_2O$): C, H, N. **63b**: oil, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (m, 6H), 2.66 (t, J = 7 Hz, 2H), 3.40 (t, J = 4.5 Hz, 4H), 3.70 (s, 3H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.39 (d, J = 9 Hz, 1H), 7.50 (m, 2H), 7.67 (d, J = 3 Hz, 1H), 8.10 (m, 1H); MS (DCI/NH_3) m/z 393 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}Cl_2N_4O$): C, H, N.

(*E*)-1-(3-Chloro-4-fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (64a) and (*Z*)-1-(3-Chloro-4-fluorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (64b). Compounds were prepared from 1-(3-chloro-4-fluorophenyl-ethanone, 1(pyridin-2-ylpiperazine and *O*-methylhydroxylamine hydrochloride by method A in 28% and 12% overall yields, respectively. **64a** maleate salt: mp 161−162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.18 (m, 12H), 3.97 (s, 3H), 6.06 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.52 (t, J = 9 Hz, 1H), 7.60 (m, 1H), 7.71 (m, 1H), 7.87 (dd, J = 7 and 3 Hz, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 377 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}FClN_4O{\cdot}C_4H_4O_4$): C, H, N. **64b** maleate salt: mp 143−144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.22 (m, 12H), 3.80 (s, 3H), 6.06 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.58 (m, 3H), 7.77 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 377 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}FClN_4O{\cdot}C_4H_4O_4{\cdot}0.2H_2O$): C, H, N.

(*E*)-1-(3,4-Dichlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one *O*-Methyloxime (65a) and (*Z*)-1-(3,4-Dichlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (65b). Compounds were prepared from 1-(3,4-dichlorophenyl)-ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 41% and 16% overall yields, respectively. **65a** maleate salt: mp 182−183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.27 (m, 12H), 3.98 (s, 3H), 6.07 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.60 (m, 1H), 7.70 (m, 2H), 7.90 (d, J = 3 Hz, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 393 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}Cl_2N_4O{\cdot}C_4H_4O_4$): C, H, N. **65b** maleate salt: mp 140−142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00 (m, 2H), 3.30 (m, 10H), 3.80 (s, 3H), 6.06 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.50 (m, 1H), 7.60 (m, 1H), 7.75 (d, J = 9 Hz, 1H), 7.80 (d, J = 3 Hz, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 393 (M + H)$^+$. Anal. Calcd ($C_{19}H_{22}Cl_2N_4O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$): C, H, N.

(*E*)-1-(4-Chloro-3-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (66a) and (*Z*)-1-(4-Chloro-3-methylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (66b). Compounds were prepared from 1-(4-chloro-3-methylphenyl)ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 47% and 16% overall yields, respectively. **66a** maleate salt: mp 177−178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.25 (m, 12H), 3.96 (s, 3H), 6.06 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.60 (m, 4H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 373 (M + H)$^+$. Anal. Calcd ($C_{20}H_{25}ClN_4O{\cdot}C_4H_4O_4{\cdot}0.6H_2O$): C, H, N. **66b** maleate salt: mp 136−137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.00 (m, 2H), 3.30 (m, 10H), 3.80 (s, 3H), 6.06 (s, 2H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.36 (m, 1H), 7.50 (m, 2H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) m/z 373 (M + H)$^+$. Anal. Calcd ($C_{20}H_{25}ClN_4O{\cdot}C_4H_4O_4{\cdot}0.6H_2O$): C, H, N.

(*E*)-1-(3,4-Dimethylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)-propan-1-one *O*-Methyloxime (67a) and (*Z*)-1-(3,4-Dimethylphenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (67b). Compounds were prepared from 1-(3,4-dimethylphenyl)-

ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 39% and 7% overall yields, respectively. **67a** maleate salt: mp 166−167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 and 2.26 (2s, 6H), 3.20 (m, 12H), 3.97 (s, 3H), 6.06 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.20 (d, J = 9 Hz, 1H), 7.40 (m, 1H), 7.46 (m, 1H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH$_3$) *m/z* 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O{\cdot}C_4H_4O_4{\cdot}0.6H_2O$): C, H, N. **67b** maleate salt: mp 130−131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 (s, 6H), 3.12 (m, 12H), 3.76 (s, 3H), 6.06 (s, 2H), 6.74 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.24 (m, 3H), 7.60 (m, 1H), 8.16 (m, 1H); MS (DCI/NH$_3$) *m/z* 353 (M + H)$^+$. Anal. Calcd ($C_{21}H_{28}N_4O{\cdot}C_4H_4O_4$): C, H, N.

1-Pyridin-3-yl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (68ab). Compound was prepared from 1-pyridin-3-ylethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 26% overall yield. 5:2 *E*:*Z* maleate salt (foam): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (m, 12H), 4.82 and 4.98 (2s, 2:5, 3H), 6.17 (s, 5H), 6.75 (m, 1H), 6.95 (d, J = 7 Hz, 1H), 7.44 (m, 1H), 7.62 (m, 1H), 7.94 and 8.07 (2m, 2:5, 1H), 8.17 (m, 1H), 8.61 and 8.65 (2m, 2:5, 1H), 8.72 and 8.90 (2m, 2:5, 1H); MS (DCI/NH$_3$) *m/z* 326 (M + H)$^+$. Anal. Calcd ($C_{18}H_{23}ClN_5O{\cdot}2.5C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(2-methyl-4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (69a) and (*Z*)-1-(4-Chlorophenyl)-3-(2-methyl-4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (69b). A solution of 2-methylpiperazine (0.50 g, 5.0 mmol) and 2-bromopyridine (5.0 mL, 50 mmol) was heated at 120 °C for 18 h. The mixture was cooled to 22 °C, diluted with water, and extracted with ethyl acetate. The organic phase was extracted with dilute aqueous HCl (2×), and the combined aqueous layers were concentrated under reduced pressure. The resulting oil was triturated with Et_2O and the solid residue was dissolved in MeOH and codistilled with dry toluene (2×) to produce 1.23 g (96%) of the desired 3-methyl-1-pyridin-2-ylpiperazine hydrobromide,14: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (d, J = 6 Hz, 3H), 3.17 (m, 2H), 3.41 (m, 3H), 4.36 (m, 2H), 6.93 (t, J = 6 Hz, 1H), 7.28 (d, J = 9 Hz, 1H), 7.90 (t, J = 8 Hz, 1H), 8.13 (dd, J = 6 and 1.5 Hz, 1H), 9.17 (br s, 1H), 9.35 (br s, 1H); MS (DCI/NH$_3$) *m/e* 178 (M + H)$^+$.

The title *E*- and *Z*-isomers were prepared from 3-chloro-1-(4-chlorophenyl)propan-1-one, 3-methyl-1-(pyridin-2-yl)piperazine, and *O*-methylhydroxylamine hydrochloride by method C in 45% and 14% overall yields, respectively. **69a**: oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.11 (d, J = 6 Hz, 3H), 2.57 (m, 2H), 2.72 (m, 2H), 2.90 (m, 4H), 3.09 (m, 1H), 3.95 (m, 1H), 3.98 (s, 3H), 3.99 (m, 1H), 6.60 (m, 1H), 6.64 (d, J = 9 Hz, 1H), 7.34 (m, 2H), 7.47 (m, 1H), 7.59 (m, 2H), 8.18 (m, 1H); MS (DCI/NH$_3$) *m/z* 373 (M + H)$^+$. **69a** maleate salt: mp 140−141 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 6 Hz, 3H), 4.00 (m, 11H), 3.97 (s, 3H), 6.08 (s, 2H), 6.72 (dd, J = 7.0 and 5 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.50 (m, 2H), 7.59 (m, 1H), 7.72 (m, 2H), 8.14 (dd, J = 5 and 1.5 Hz, 1H); Anal. Calcd ($C_{20}H_{25}ClN_4O{\cdot}C_4H_4O_4$): C, H, N. **69b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (d, J = 6 Hz, 3H), 2.22 (m, 1H), 2.33 (m, 2H), 2.68 (m, 4H), 2.83 (m, 1H), 2.96 (m, 1H), 3.72 (s, 3H), 3.85 (d, J = 12 Hz, 2H), 6.61 (d, J = 7 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 7.48 (m, 5H), 8.1 (m, 1H); MS (DCI/NH$_3$) *m/z* 373 (M + H)$^+$. **69b** maleate salt: foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, J = 6 Hz, 3H), 3.69 (m, 11H), 3.80 (s, 3H), 6.09 (s, 2.4H), 6.73 (dd, J = 7 and 5 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.58 (m, 5H), 8.15 (dd, J = 5 and 1.5 Hz, 1H); Anal. Calcd ($C_{20}H_{25}ClN_4O{\cdot}1.2C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propan-1-one *O*-Methyloxime (70a) and (*Z*)-1-(4-Chlorophenyl)-3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propan-1-one *O*-Methyloxime (70b). The title *E*- and *Z*-isomers were prepared from 3-chloro-1-(4-chlorophenyl)propan-1-one, 1′,2′,3′,4′,5′,6′-hexahydro[2,4′]bipiridinyl hydrochloride,[18,35,36] and *O*-methylhydroxylamine hydrochloride by method C in 21% and 7% overall yields, respectively. **70a**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 4H), 2.05 (m, 2H), 2.45 (t, J = 7.5 Hz, 2H), 2.61 (m, 1H), 2.92 (m, 4H), 3.92 (s, 3H,), 7.19 (dd, J = 7.5 and 6 Hz, 1H), 7.26 (d, J = 9 Hz, 1H), 7.47 (m, 2H), 7.69 (m, 3H), 8.48 (m, 1H); MS (DCI−NH$_3$) *m/z* 358 (M + H)$^+$. Anal. Calcd for **70a** maleate salt (foam) ($C_{20}H_{24}ClN_3O{\cdot}C_4H_4O_4$): C, H, N. **70b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (m, 4H), 1.98 (m, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.60 (m, 1H), 2.68 (t, J = 7.5 Hz, 2H), 2.88 (m, 2H), 3.71 (s, 3H,), 7.19 (dd, J = 7.5 and 6 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.45 (m, 4H), 7.69 (m, 1H), 8.48 (m, 1H); MS (DCI−NH$_3$) *m/z* 358 (M + H)$^+$. Anal. Calcd ($C_{20}H_{24}ClN_3O{\cdot}0.1H_2O$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propan-1-one *O*-Methyl-oxime (71a) and (*Z*)-1-(4-chlorophenyl)-3-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]-bipyridinyl-1′-yl)propan-1-one *O*-Methyloxime (71b). Compounds were synthesized from the hydrochloride salt of 1′,2′,3′,4′,5′,6′-hexahydro-[2,4′]bipyridinyl 1-oxide,[18] 3-chloro-1-(4-chlorophenyl)-propan-1-one, and *O*-methylhydroxylamine by method C in 41% and 7% yields, respectively. **71a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (m, 2H), 1.88 (m, 2H), 2.08 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7 Hz, 1H), 2.93 (m, 5H), 3.21 (m, 1H), 3.92 (s, 3H), 7.28 (m, 2H), 7.38 (m, 1H), 7.48 (d, J = 9 Hz, 2H), 7.68 (d, J = 9 Hz, 2H); 8.24 (m, 1H); MS (DCI/NH$_3$) *m/z* 374 (M + H)$^+$. Anal. Calcd for **71a** maleate salt (foam) ($C_{20}H_{24}ClN_3O_2{\cdot}C_4H_4O_4$): C, H, N. **71b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (m, 2H), 1.89 (m, 2H), 2.00 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 3.21 (m, 1H), 3.72 (s, 3H), 7.30 (m, 2H), 7.38 (m, 2H), 7.45 (d, J = 4.5 Hz, 2H), 7.49 (m, 1H); 8.21 (m, 1H); MS (DCI/NH$_3$) *m/z* 374 (M + H)$^+$. Anal. Calcd for **71b** maleate salt (foam) ($C_{20}H_{24}ClN_3O_2{\cdot}C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)propan-1-one *O*-Methyloxime (72a). Compound **72a** was synthesized from *tert*-butyl-3-oxo-1-piperidinecarboxylate[36,37] by the process described for the synthesis of **70a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.63 (m, 3H), 1.79 (m, 1H), 1.97 (m, 1H), 2.15 (m, 1H), 2.26 (t, J = 7.5 Hz, 1H), 2.59 (m, 2H), 2.95 (m, 3H), 3.12 (m, 1H), 3.97 (s, 3H), 7.13 (m, 2H), 7.35 (d, J = 9 Hz, 2H), 7.58 (d, J = 9 Hz, 2H), 7.63 (m, 1H), 8.57 (m, 1H); MS (DCI/NH$_3$) *m/z* 358 (M + H)$^+$. Anal. Calcd ($C_{20}H_{24}ClN_3O{\cdot}0.25H_2O$): C, H, N.

(*E*)-1-(4-Fluorophenyl)-2-(4-pyridin-2-yl)ethanone Oxime (73a) and (*Z*)-1-(4-Fluorophenyl)-2-(4-pyridin-2-yl)ethanone Oxime (73b). Compounds were prepared from 2-chloro-1-(4-fluorophenyl)-ethanone, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method D in 34% and 4% overall yields, respectively. 73a: mp 136−137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.46 (m, 4H), 3.38 (m, 6H), 6.60 (dd, J = 7 and 4 Hz, 1H), 6.76 (d, J = 9 Hz, 1H), 7.20 (t, J = 9 Hz, 2H), 7.50 (m, 1H), 7.62 (m, 2H), 8.09 (m, 1H), 11.05 (s, 1H); MS (DCI/NH$_3$) *m/z* 315 (M + H)$^+$. **73b**: mp 136−138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (m, 4H), 3.60 (t, J = 4 Hz, 4H), 3.66 (s, 2H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.77 (d, J = 9 Hz, 1H), 7.20 (t, J = 9 Hz, 1H), 7.50 (m, 1H), 7.62 (m, 2H), 8.09 (m, 1H), 11.45 (s, 1H); MS (DCI/NH$_3$) *m/z* 315 (M + H)$^+$. Anal. Calcd ($C_{17}H_{19}FN_4O{\cdot}0.3H_2O$): C, H, N.

(*E*)-1-(4-Fluorophenyl)-2-(4-pyridin-2-yl)ethanone *O*-Methyloxime (74a) and (*Z*)-1-(4-Fluorophenyl)-2-(4-pyridin-2-yl)ethanone *O*-Methyloxime (74b). Compounds were prepared from 2-chloro-1-(4-fluorophenyl)ethanone, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method D in 17% and 6% overall yields, respectively. **74a** dimaleate salt: mp 152−153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 10H), 3.86 (s, 3H), 6.20 (s, 4H), 6.70 (dd, J = 7 and 4 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 7.30 (t, J = 9 Hz, 2H), 7.60 (m, 1H), 7.68 (m, 2H), 8.12 (m, 1H); MS (DCI/NH$_3$) *m/z* 329 (M + H)$^+$. Anal. Calcd ($C_{18}H_{21}FN_4O{\cdot}2.0C_4H_4O_4{\cdot}1.2H_2O$): C, H, N. **74b** dimaleate salt: mp 144−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 10H), 3.97 (s, 3H), 6.20 (s, 4H), 6.70 (dd, J = 7 and 4 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 7.30 (t, J = 9 Hz, 2H), 7.58 (m, 1H), 7.85 (m, 2H), 8.13 (m, 1H); MS (DCI/NH$_3$) *m/z* 329 (M + H)$^+$. Anal. Calcd ($C_{18}H_{21}FN_4O{\cdot}2.0C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Fluorophenyl)-4-(4-pyridin-2-ylpiperazin-1-yl)butan-1-one Oxime (75a) and (*Z*)-1-(4-Fluorophenyl)-4-(4-pyridin-2-

ylpiperazin-1-yl)butan-1-one Oxime (75b). Compounds were prepared from 4-chloro-1-(4-fluorophenyl)butan-1-one, 1-pyridin-2-ylpiperazine, and hydroxylamine hydrochloride by method D in 35% and 4% overall yields, respectively. **75a**: mp 158–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.40 (m, 4H), 2.75 (t, J = 7 Hz, 2H), 3.43 (m, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.51 (m, 1H), 7.72 (dd, J = 9 and 4 Hz, 2H), 8.10 (m, 1H), 11.07 (s, 1H); MS (DCI/NH$_3$) m/z 343 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}FN_4O{\cdot}0.5H_2O$): C, H, N. **75b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55 (m, 2H), 2.30 (t, J = 7 Hz, 2H), 2.35 (t, J = 4.5 Hz, 4H), 2.53 (m, 2H), 3.42 (t, J = 4.5 Hz, 4H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.52 (m, 3H), 8.09 (m, 1H), 10.64 (s, 1H); MS (DCI/NH$_3$) m/z 343 (M + H)$^+$.

(*E*)-1-(4-Fluorophenyl)-4-(4-pyridin-2-ylpiperazin-1-yl)butan-1-one *O*-Methyloxime (76a) and (*Z*)-1-(4-Fluorophenyl)-4-(4-pyridin-2-ylpiperazin-1-yl)butan-1-one *O*-Methyloxime (76b). Compounds were prepared from 4-chloro-1-(4-fluorophenyl)butan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method D in 43% and 18% overall yields, respectively. **76a**: mp 55–56 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.38 (t, J = 4.5 Hz, 4H), 2.75 (t, J = 7 Hz, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.91 (s, 3H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.51 (m, 1H), 7.72 (dd, J = 9 and 4 Hz, 2H), 8.10 (m, 1H); MS (DCI/NH$_3$) m/z 357 (M + H)$^+$. Anal. Calcd ($C_{20}H_{25}FN_4O$): C, H, N. **76b**: oil, ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55 (quintet, J = 7 Hz, 2H), 2.30 (t, J = 7 Hz, 2H), 2.37 (t, J = 4.5 Hz, 4H), 2.55 (m, 2H), 3.42 (t, J = 4.5 Hz, 4H), 3.72 (s, 3H), 6.61 (dd, J = 7 and 4 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 7.22 (t, J = 9 Hz, 2H), 7.50 (m, 3H), 8.09 (m, 1H); MS (DCI/NH$_3$) m/z 357 (M + H)$^+$.

(*E*)-1-(4-Chlorophenyl)-2-hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (77a) and (*Z*)-1-(4-Chlorophenyl)-2-hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (77b). 1-(4-Chlorophenyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one (522 mg, 1.6 mmol) and iodobenzene diacetate [PhI(OAc)$_2$, 547 mg, 1.7 mmol) were combined in methanol (25 mL), and a solution of KOH (297 mg, 5.3 mmol) in MeOH (5 mL) was added dropwise. The reaction was continued at room temperature for 5 h and then was concentrated under reduced pressure. The residue was treated with ethyl acetate and water, and the organic layer was separated, washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to afford 570 mg of crude 1-(4-chlorophenyl)-1,1-dimethoxy-3-(4-pyridin-2-ylpiperazin-1-yl)propan-2-ol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (m, 4H), 3.13 (s, 3H), 3.20 (s, 3H), 3.41 (m, 6H), 4.05 (m, 1H), 4.78 (d, J = 6 Hz, 1H), 6.60 (dd, J = 7 and 4.5 Hz, 1H), 6.77 (d, J = 9 Hz, 1H), 7.40 (s, 4H), 7.50 (m, 1H), 8.08 (m, 1H); MS (DCI/NH$_3$) m/z 392 (M + H)$^+$.

The crude 1-(4-chlorophenyl)-1,1-dimethoxy-3-(4-pyridin-2-ylpiperazin-1-yl)propan-2-ol (570 mg, ~1.5 mmol) was dissolved in chloroform (20 mL) and treated at room temperature with 5% H_2SO_4 (15 mL) for 18 h. After a saturated solution of NaHCO$_3$ was added, the organic layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to afford 345 mg of crude 1-[4-chloro-2-hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)]propanon-1-one: MS (DCI/NH$_3$) m/z 346 (M + H)$^+$.

Methoxylamine hydrochloride (410 mg, 5 mmol) and crude 1-[4-chloro-2-hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)]propanon-1-one (344 mg, ~1 mmol) were combined in pyridine (10 mL) and the reaction was left at room temperature for 14 h. The pyridine was removed under reduced pressure, and the residue was treated with a saturated solution of NaHCO$_3$ and extracted with ethyl acetate. The acetate layer was washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (CH$_2$Cl$_2$/acetone 4:1 as eluent) to provide 200 mg (53%) of *E*-isomer (77a) and 132 mg (35%) of *Z*-isomer (77b). **77a** maleate salt: mp 155–156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 10H), 3.78 (s, 3H), 4.85 (m, 1H), 6.06 (s, 2H), 6.72 (dd, J = 7 and 4.5 Hz, 1H), 6.91 (d, J = 7 Hz, 1H), 7.44 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 1H), 7.60 (m, 1H), 8.15 (m, 1H); MS (DCI/NH$_3$) m/z 375 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O_2{\cdot}C_4H_4O_4$): C, H, N. **77b** maleate salt: mp 167–169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 10H), 3.95 (s, 3H), 4.35 (m, 1H), 5.56 (br d, J = 7 Hz, 1H), 6.11 (s, 3H), 6.74 (dd, J = 7 and 4.5 Hz, 1H), 6.93 (d, J = 7 Hz, 1H), 7.48 (d, J = 9 Hz, 2H), 7.60 (m, 1H), 7.70 (d, J = 9 Hz, 1H), 8.15 (m, 1H); MS (DCI/NH$_3$) m/z 375 (M + H)$^+$. Anal. Calcd ($C_{19}H_{23}ClN_4O_2{\cdot}1.5C_4H_4O_4$): C, H, N.

(*E*)-1-(4-Chlorophenyl)-2-methoxy-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (78a) and (*Z*)-1-(4-Chlorophenyl)-2-methoxy-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (78b). Compounds were isolated as side products of process for the synthesis of 77a and 77b in 2% and 3% yields, respectively. **78a**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.56 (m, 5H), 2.80 (dd, J = 12 and 6 Hz, 1H), 3.14 (s, 3H), 3.42 (t, J = 6 Hz, 4H), 3.94 (s, 3H), 5.05 (dd, J = 7 and 4.5 Hz, 1H), 6.62 (dd, J = 7 and 4.5 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.50 (m, 3H), 7.68 (d, J = 9 Hz, 1H), 8.08 (m, 1H); MS (DCI/NH$_3$) m/z 389 (M + H)$^+$. Anal. Calcd ($C_{20}H_{25}ClN_4O_2$): C, H, N. **78b**: oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (m, 4H), 2.40 (dd, J = 12 and 6 Hz, 1H), 2.55 (m, 1H), 3.35 (s, 3H), 3.42 (m, 4H), 3.76 (s, 3H), 4.17 (t, J = 7 Hz, 1H), 6.62 (dd, J = 7 and 4.5 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.34 (d, J = 9 Hz, 2H), 7.50 (m, 3H), 8.10 (m, 1H); MS (DCI/NH$_3$) m/z 389 (M + H)$^+$. Anal. Calcd ($C_{20}H_{25}ClN_4O_2$): C, H, N.

(*E*)-2-Hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)-propan-1-one Oxime (79a) and (*Z*)-2-Hydroxy-3-(4-pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one Oxime (79b). Compounds **79a** and **79b** were prepared from 3-(4-pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one by the process described for the synthesis of **77a** and **77b** in 10% and 8% overall yields, respectively. **79a**: mp 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s + m, 7H), 2.52 (m, 2H), 3.42 (m, 4H), 4.52 (m, 1H), 5.20 (d, J = 4 Hz, 1H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.16 (m, 3H), 7.22 (t, J = 7 Hz, 1H), 7.50 (m, 1H), 8.10 (m, 1H), 10.60 (s, 1H); MS (ESI+) m/z 341 (M + H)$^+$; MS (ESI−) m/z 339 (M − H)$^-$. Anal. Calcd ($C_{19}H_{24}N_4O_2$): C, H, N. **79b**: mp 157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.55 (m, 5H), 2.66 (dd, J = 12 and 7 Hz, 1H), 3.44 (m, 4H), 5.18 (m, 1H), 5.44 (m, 1H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.14 (m, 1H), 7.22 (t, J = 7 Hz, 1H), 7.45 (m, 2H), 7.51 (m, 1H), 8.10 (m, 1H), 11.20 (s, 1H); MS (ESI+) m/z 341 (M + H)$^+$; MS (ESI−) m/z 339 (M − H)$^-$. Anal. Calcd ($C_{19}H_{24}N_4O_2$): C, H, N.

(*E*)-2-Methoxy-3-(4-pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)-propan-1-one *O*-Methyloxime (80a) and (*Z*)-2-Methoxy-3-(4-pyridin-2-ylpiperazin-1-yl)-1-(*m*-tolyl)propan-1-one *O*-Methyloxime (80b). Compounds were isolated as side products of process for the synthesis of **79a** and **79b** in 2% and 1% yields, respectively. **80a**: oil, 1% overall yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.38 (m, 4H), 2.85 (s, 2H), 3.20 (s, 3H), 3.30 (m, 5H), 6.60 (dd, J = 7 and 4 Hz, 1H), 6.74 (d, J = 7 Hz, 1H), 7.10 (m, 1H), 7.20 (m, 3H), 7.46 (m, 1H), 8.05 (m, 1H), 11.10 (s, 1H); MS (ESI+) m/z 355 (M + H)$^+$; MS (ESI−) m/z 353 (M − H)$^-$. **80b**: oil, 2% overall yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.53 (m, 5H), 2.80 (dd, J = 12 and 7 Hz, 1H), 3.15 (s, 3H), 3.44 (m, 4H), 5.18 (q, J = 3 Hz, 1H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.14 (m, 1H), 7.22 (t, J = 7 Hz, 1H), 7.45 (m, 2H), 7.51 (m, 1H), 8.10 (m, 1H), 11.44 (s, 1H); MS (ESI+) m/z 355 (M + H)$^+$; MS (ESI−) m/z 353 (M − H)$^-$. Anal. Calcd ($C_{20}H_{26}N_4O_2{\cdot}0.15CH_2Cl_2$): C, H, N.

1-(4-Chlorophenyl)-2-methyl-3-(4-pyridin-2-ylpiperazin-1-yl)-propanon-1-one *O*-Methyloxime (81ab). Compound was prepared from 1-(4-chlorophenyl)propan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 18% overall yield, as a 3:1 mixture of *Z*:*E* isomers: dimaleate salt, mp 152–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 and 1.28 (2 d, 3:1, J = 7 Hz, 3H), 3.30 (m, 11H), 3.78 and 3.92 (2 s, 3:1, 3H), 6.18

(s, 4H), 6.73 (m, 1H), 6.93 (m, 1H), 7.50 (m, 5H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 373 $(M+H)^+$. Anal. Calcd ($C_{20}H_{25}ClN_4O\cdot 2.0C_4H_4O_4$): C, H, N.

1-(4-Chlorophenyl)-2-(methoxyaminomethyl)-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (82a). Compound was prepared from 3-chloro-1-(4-chlorophenyl)propan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 25% overall yield, as a 1:1 mixture of *Z*:*E* isomers: maleate salt, mp 118−121 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (m + 2s, 13H), 3.70 (m + 2s, 6H), 6.18 (s, 3.5H), 6.75 (m, 1H), 6,95 (m, 1H), 7.50 (m, 3H), 7.60 (m, 1H), 7.75 (m, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 418 $(M + H)^+$. Anal. Calcd ($C_{21}H_{28}ClN_5O_2\cdot 1.75C_4H_4O_4$): C, H; N calcd 11.28, found 10.86.

1-(4-Chlorophenyl)-2-isopropoxymethyl-3-(4-pyridin-2-ylpiperazin-1-yl)propanon-1-one *O*-Methyloxime (83a). Compound was prepared from 3-chloro-1-(4-chlorophenyl)propan-1-one, 1-pyridin-2-ylpiperazine, and *O*-methylhydroxylamine hydrochloride by method A in 35% overall yield, as a 2:1 mixture of *Z*:*E* isomers: dimaleate salt, mp 106−109 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (m, 6H), 3.40 (m, 20H), 3.80 (s, 2H), 3.92 (s, 1H), 6.18 (s, 4H), 6.75 (m, 1H), 6,95 (m, 1H), 7.50 (m, 5H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 431 $(M + H)^+$. Anal. Calcd ($C_{23}H_{31}ClN_4O_2\cdot 2.0C_4H_4O_4$): C, H, N.

2-Hydroxy-1-pyridin-3-yl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one *O*-Methyloxime (84ab). Compound was prepared from 1-pyridin-3-yl-3-(4-pyridin-2-ylpiperazin-1-yl)propan-1-one by the process described for the synthesis of **77a** and **77b** in 13% overall yield as a 2:1 mixture of *Z*:*E* isomers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (m, 2.5H), 2.55 (m, 3.2 H), 3.71 (dd, J = 12 and 7 Hz, 0.3H), 3.42 (m, 4H), 3.75 (s, 2H), 3.92 (s, 1H), 4.57 (m, 0.66H), 5.36 (m, 0.34H), 5.52 (d, J = 4 Hz, 0.34H), 5.60 (d, J = 4 Hz, 0.66H), 6.62 (dd, J = 7 and 4 Hz, 1H), 6.80 (d, J = 7 Hz, 1H), 7.42 (m, 1H), 7.53 (m, 1H), 7.75 (dt, J = 7 and 2 Hz, 0.66H), 8.04 (dt, J = 7 and 2 Hz, 0.34H), 8.10 (m, 1H), 8.54 (m, 1.66H), 8.78 (m, 0.33H); MS (ESI+) *m/z* 342 $(M + H)^+$. Anal. Calcd ($C_{18}H_{23}N_5O_2\cdot 0.5H_2O$): C, H; N calcd 19.99, found 19.53.

2-(4-Pyridin-2-ylpiperazin-1-ylmethyl)-3,4-dihydro-2*H*-naphthalen-1-one *O*-Ethyloxime (85a). Compound was prepared from 3,4-dihydro-2*H*-naphthalen-1-one, 1-pyridin-2-ylpiperazine, and *O*-ethylhydroxylamine hydrochloride by method A in 15% overall yield: dimaleate salt, mp 146−147 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, J = 7 Hz, 3H), 1.87 (m, 1H), 2.10 (m, 1H), 2.73 (m, 1H), 3.25 (m, 11H), 3.97 (m, 1H), 4.22 (q, J = 7 Hz, 2H), 6.15 (s, 4H), 6.73 (dd, J = 7 and 4 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 7.23 (m, 2H), 7.33 (m, 1H), 7.60 (m, 1H), 7.90 (d, J = 9 Hz, 1H), 8.16 (m, 1H); MS (DCI/NH_3) *m/z* 365 $(M + H)^+$. Anal. Calcd ($C_{22}H_{28}N_4O\cdot 2.0C_4H_4O_4$): C, H, N.

Biological Procedures: (A) FLIPR Assay of Receptor Activation by Agonists. Test compounds were evaluated for their ability to activate the human $D_{4.4}$ receptor coexpressed with $G\alpha_{qo5}$ in HEK293 cells according to the method described by Moreland et al.[39]

(B) $D_{4.4}$ Calcium Flux Assay (Antagonist Mode). Compounds were evaluated by the procedure described above with the following addition. After the final fluorescence reading in agonist mode, another 50 μL from the dopamine plate was added to the cells to make the final concentration 1 μM. Fluorescence readings were continued for an additional 3 min. The data were normalized with the response of 1 μM dopamine alone.[39]

(C) D_{2L} and $D_{4.4}$ Radioligand Binding Assays. Dopamine D_{2L} and D_4 ligand binding affinities were determined by use of radioligands [^{125}I]-PIPAT and [^{3}H]-A-369508, respectively, as described by Moreland et al.[39]

(D) Conscious Rat Penile Erection Model. Male Wistar rats were used as a primary animal model to study penile erection in vivo.[47] All experiments were carried out between 9:00 a.m. and 3:00 p.m. in a diffusely illuminated testing room with a red light. Animals were weighed and allowed to adapt to the testing room for 60 min prior to the beginning of experiments. Rats were placed individually in a transparent cage (20 × 30 × 30 cm) after drug injection. The number of penile erections was recorded by direct observation for a period of 60 min after drug dosing, and the number of animals exhibiting one or more erections was expressed as incidence (percent).

(E) Emesis Model in Ferrets. Male Fitch ferrets (body weights 1.0−1.5 kg, Marshall Farms) were fasted overnight before experimentation. Test compounds were administrated subcutaneously, and animals were carefully placed in individual observation cages and watched for any signs of drug-induced emesis and signs of nausea for 90 min. Nausea was characterized by behaviors such as licking, gagging, backing, head burying, and intense abdominal grooming. When present, emesis was usually preceded by these behaviors and was characterized by rhythmic abdominal contractions which were associated with vomiting or retching movement.

Supporting Information Available: Elemental analysis data for the compounds and X-ray crystallographic information for compounds **22a**, **25a**, **39a**, and **75a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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